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**USING LUNG VOLUME RECRUITMENT THERAPY TO
IMPROVE SWALLOWING AND AIRWAY PROTECTION IN
INDIVIDUALS WITH AMYOTOPHIC LATERAL SCLEROSIS**

by

Stuart James Cleary

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in
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Examining Committee

John Misiaszek, Occupational Therapy

Sharon Warren, Rehabilitation Medicine

Wendy Johnston, Medicine

K. Ming Chan, Centre for Neuroscience

Kathryn Yorkston, Rehabilitation Medicine, University of Washington

Abstract

Lung volume recruitment (LVR) is a manual insufflation technique used to help patients with amyotrophic lateral sclerosis (ALS) cough with sufficient force to clear pulmonary secretions. LVR has been associated with positive treatment outcomes; however much of the evidence for its use is anecdotal and many questions remain about the nature of the treatment effect. The purpose of this study was to answer the following research questions: (1) What is the intensity and duration of the LVR treatment effect on standard tests of pulmonary function? (2) Does LVR improve volitional airway clearance behaviours (i.e., hawking, throat clearing, unassisted coughing and forced expiration)? (3) What is the effect of LVR on a specific compensatory swallowing technique (the supraglottic swallow maneuver)? (4) What are participants' perspectives on the effects of LVR on their respiration and secretion management?

Participants were 29 individuals with ALS who were currently doing LVR. The study involved a within-subjects, repeated measures cross-over research design. Measurements were collected on each participant under two conditions: LVR treatment and no treatment. The order of these conditions was counterbalanced to control for order effects. Assessments of pulmonary function, coughing, airway clearance and swallowing were conducted at three time points: baseline, during treatment, and 30 minutes after the treatment was provided.

The results of this thesis study were as follows: 1) LVR had a significant positive effect on FVC immediately post-treatment but did not have a facilitative effect on SnP at any time point; 2) LVR had a significant positive effect on

unassisted coughing, hawking, throat clearing, and forced expiration at time 2 (immediately after treatment) and time 3 (30 minutes post treatment); 3) LVR had a significant positive effect on PCF measured during the supraglottic swallow maneuver, immediately after and 30 minutes post-treatment; 4) The majority of participants expressed satisfaction with LVR, indicating that they tolerated the treatment well, and that they perceived positive effects on cough strength and the ability to clear the airway. A minority of participants agreed that LVR lessened their fear and anxiety about choking. Findings have important clinical implications for the symptom management of individuals with ALS. In addition, the results help inform theoretical models of mechanisms of the LVR treatment effect.

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Introduction

Amyotrophic Lateral Sclerosis – Epidemiology and risk factors

Amyotrophic Lateral Sclerosis (ALS) is an acquired, age-related, degenerative motor neuron disease. It is the most common form of adult motor neuron disease, affecting approximately 3,000 Canadians (Statistics Canada, 2003) and the world-wide prevalence is estimated at 1.8 to 2.1 per 100,000 (Strong, 2004). Onset typically occurs between 50 and 60 years of age, although 30% of patients will develop symptoms before the age of 45. The vast majority of cases (90-95%) are considered sporadic and idiopathic, with familial ALS, the inherited form, accounting for 5-10% of cases (Wills & Brown, 2006). ALS is rapidly progressive: approximately 50% of affected individuals die within three years of diagnosis and 90% die within five years. Those who develop symptoms before the age of 45 tend to live approximately three years longer than those with an onset of symptoms after the age of 45 years (Strong, 2004). The age of onset of familial ALS tends to be 15-20 years younger than in sporadic cases (Nelson & McGuire, 2006). In both sporadic and familial ALS, age of onset is approximately 5 years earlier for men than for women, and men are more likely to develop ALS than women, with a male:female prevalence ratio of 1.6:1 (Nelson & McGuire, 2006).

Although the cause of sporadic ALS remains unknown and is likely multifactorial, certain risk factors have been identified, including the following: exposure to neurotoxins (i.e., lead, mercury, insecticides, herbicides, and solvents); engagement in specific occupations (i.e., electrical worker, farmer, heavy manual labor); history of musculoskeletal trauma and electrical shock; physical prowess; and

lifestyle factors such smoking and the intake of dietary glutamate (Nelson & McGuire, 2006).

Researchers have conducted epidemiological studies with participants from carefully delineated populations in an effort to identify risk factors for the development of ALS. The implication of exogenous neurotoxins as a significant risk factor for ALS was supported by research on the Western Pacific form of the disease. On the island of Guam in the 1950s, males had an unusually high incidence of ALS (i.e., 50-100 times higher than the world incidence) that indicated potential for an environmental cause (Reed & Brody, 1975). Researchers have shown that these cases were likely caused by ingestion of the cycad nut, which contains a neurotoxin (Barceloux, 2008).

A combination of other risk factors, including exogenous and endogenous agents, has been identified in other studies. US Gulf War veterans have twice the incidence of ALS when compared to non-deployed military personnel, and exposure to factors such as nerve gases like sarin, vaccinations and military stress have been considered as potential causative agents (Haley, 2003).

Neuropathology

ALS is characterized by progressive degeneration of motor neurons and descending motor tracts. There is a loss of lower motor neurons in the anterior horn of the spinal cord and motor nuclei of cranial nerves V, VII, X, XI, XII. Large pyramidal upper motor neurons in the motor cortex are damaged and axons in corticobulbar and corticospinal tracts degenerate. Given the selective involvement of this system, it has been hypothesized that properties inherent in motor neurons make

them preferentially susceptible to ALS (Weber, 2006). Motor neuron size, length, volume of neuronal processes, high metabolic demands and unique electrical proprieties may predispose them to excitotoxicity, oxidative injury, cytoskeletal disruption, and the loss of neurotrophic support (Nelson & McGuire, 2006; Shaw, 2006).

No one of these proposed mechanisms is thought to cause ALS on its own. Among scientists there is a consensus that the neuropathology of ALS is complex, multi-factorial and involves multiple cell types and cellular processes within and outside of the motor system (Eisen, 1995; Strong 2004). It is likely that some mechanisms are more causative than others. Also, some of the mechanisms that are considered causative may actually be by-products of co-occurring pathogenic processes (Wills & Brown, 2006).

Clinical Course

ALS is increasingly recognized as a syndrome because of the heterogeneous biological nature of the disorder and the variable way it manifests in each patient (Strong, 2003). However, there are commonalities in nature and progression of symptoms, and two primary sub-types of ALS are described in the literature. These sub-types are based on the site of initial presentation of signs and symptoms and are referred to as limb onset and bulbar onset ALS.

The limb onset sub-type of ALS accounts for approximately 70% of cases and involves spinal symptoms affecting upper and lower extremity function due to degeneration of the corticospinal tracts and/or the loss of motor neurons in the spinal anterior horn, ventral roots and peripheral nerves within the cervical, thoracic and

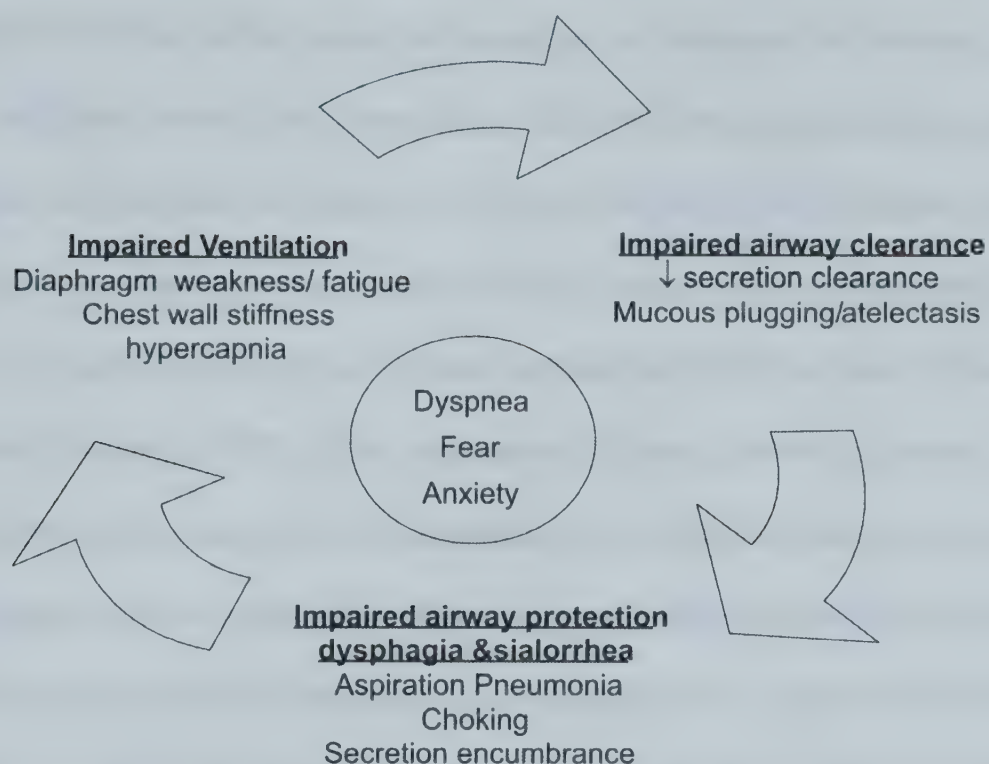
lumbar regions (Mitsumoto, 2009; Yorkston, Miller & Strand, 1995). The bulbar onset sub-type of ALS accounts for the remaining 30% percent of cases and is associated with early speech and swallowing difficulty as a result of degeneration of the corticobulbar tracts and/or involvement of the motor nuclei of cranial nerves V, VII, IX, X and XII in the brainstem (Mitsumoto, 2009; Yorkston, Miller & Strand, 1995).

Strong (2004) examined the demographic characteristics of 773 patients with ALS in southwestern Ontario from 1985-2004 and found that patients affected by the limb onset sub-type generally experienced a slower rate of disease progression and lived longer than patients with bulbar-onset ALS (i.e., an average of 52 months life expectancy post diagnosis versus 35 months for individuals with bulbar onset ALS).

Despite differences in disease progression and initial presentation, patients with both types of ALS present with a combination of upper and lower motor neuron pathology which manifests in a combination of weakness, atrophy, spasticity, and abnormal (hyperactive and/or absent) reflexes. Also, in both types of ALS, respiration is significantly affected. If left untreated, three main factors may prematurely predispose affected individuals to respiratory failure and, ultimately, death: impaired ventilation, impaired airway clearance and impaired airway protection and dysphagia (Benditt, 2006; Perrin, Uterborn, Ambrosio & Hill, 2004). A triad of inter-related factors lead to neuromuscular failure and compromise quality of life (see Figure 1).

This cycle of inter-related respiratory conditions is amenable to treatment (Miller et al., 1999; 2009). Rehabilitative approaches, such as lung volume recruitment therapy (LVR), may help preserve functional abilities and stave off

respiratory failure. Any effective respiratory treatment should address ventilation, airway clearance of secretions, airway protection and dysphagia. Each of these components will be reviewed in the sections that follow.



(Adapted from Benditt, 2006)

Figure 1. Conceptual model of neuromuscular respiratory failure in ALS.

Respiration in ALS: Ventilation

The primary function of breathing is gas exchange. Gas exchange is accomplished by two intertwined respiratory systems: the ventilatory pump and lung function (Shapiro, Harrison, Kacmarek & Cane, 1985). The ventilatory pump is responsible for moving gas in and out of the lungs. The chest wall and the muscles of ventilation (primarily the diaphragm) work to support lung function by creating sufficient force across the trans-pulmonary pressure gradient (from the plural space to

the mouth) for adequate flow and volume. This pressure differential assists in the diffusion of gas across the alveolar-capillary membrane and drives the exchange of gas between pulmonary blood flow and the atmosphere (West, 2000).

Respiratory flow, pressure and airway resistance are often affected relatively early in ALS. Flow is the quantity of molecules (or volume of air) moving per unit time (milliliters/second) and the amount of flow is directly proportional to the change in pressure between two compartments (Baken & Orkoff, 2000). Pressure is the force applied by a molecule per unit area; it is directly proportional to the number of molecules and temperature and inversely proportional to the volume of the container (Baken & Orkoff, 2000). When the pressure differential between the two compartments increases, the flow increases commensurately. Gas moves from areas of higher pressure to areas of lower pressure and the rate of flow is determined by the pressure gradient and the resistance to flow (Shapiro et al., 1985). Resistance refers to the frictional forces that oppose the movement of airflow to and from the lungs. Airway resistance (R_{aw}) is defined as the pressure gradient between the alveoli and the mouth divided by rate of airflow ($\Delta P_{cmH_2O}/\Delta VL/sec$); a normal value in adults is 0.5 to 1.5 cmH₂O/L/sec (Cotes, 1993).

Ventilation is defined as the process by which gas moves to the gas exchange areas of the terminal bronchioles (i.e., respiratory bronchioles, alveolar ducts and alveolar sacs). Researchers have noted regional differences in the effectiveness of air exchange in the lungs with the lung bases being approximately 30% more effective than the apex or upper zones of the lungs (West, 2000). This means that there is always some residual air (~ 150 ml) in the airways from each previous breath. This

residual air contains a higher concentration of CO₂. The proportion of 'fresh gas' available for exchange drops as ventilatory pump function becomes less efficient (West, 2000). As less CO₂ is blown off with each breath, tidal volumes or respiratory frequency (or both) must be increased to prevent high levels of CO₂ from being retained within the body.

Ventilation impairment in ALS is described as a restrictive pattern caused by a compromised ventilatory pump function that is characterized by hypoventilation and reduced lung capacities (West, 2001). Neuromuscular induced weakness and wasting of the diaphragm diminishes intra-thoracic pressure generation, limits chest wall expansion during inspiration and reduces elastic recoil forces during expiration (Ballard, 2002). Neuromuscular changes to the chest wall cause it to become progressively stiffer over time secondary to disuse atrophy, spasticity, contractures and adhesions which create resistance, reduce range of motion and increase the mechanical forces required to accomplish adequate ventilation (Perrin et al., 2004).

The airways and lung parenchyma also become less compliant over time and more trans-pulmonary pressure is required to exchange a given volume of gas (West, 2001). With a normal tidal breath of about 500 ml, distending pressure required to move gas through the airway is typically <3 cm/H₂O pressure for a normal airflow rate of 1L/sec (West, 2000). As a point of comparison, when patients with ALS begin to present with symptoms of respiratory insufficiency, the distending pressure required for adequate gas exchange is often 3 – 5 times the normal value (Wilkins, Stoller & Scanlan, 2003).

Accessory muscles of inspiration are increasingly recruited to assist with normal tidal breathing and the increased work of breathing may also lead to diaphragm fatigue. As the diaphragm fatigues, less contractile force is generated during inhalation and more CO₂ retained within the system. A detrimental cycle develops as retained CO₂ further impairs diaphragm contractility (West, 2001). Many patients can experience mild to moderate degrees of hypoventilation, but their lung volumes remain within a relatively normal range. Miller et al. (1999) report that the early symptoms of dyspnea or perceived shortness of breath and hypoventilation are subtle, are often not reported by patients and are easily overlooked during a clinical exam. As ALS progresses, hypercapnia typically develops as a pre-terminal event (Vittaca et al., 1997) caused by several inter-related factors including the increased work of breathing, inefficient breathing mechanics (i.e., rapid, shallow breathing) respiratory muscle fatigue and reduced central neural respiratory drive (Ballard, 2002).

Respiratory failure may occur at any time in the later stages of the disease; 96% of ALS deaths are cardiopulmonary in nature (Yorkston, 2004; Neudert, Oliver, Wasner & Borasio, 2001). Death ensues as a result of medical complications associated with hypoventilation, CO₂ retention within the body, and pneumonia. As functional vital capacity (FVC) drops below 50% and/or patients become symptomatic (i.e., dyspnea upon exertion, orthopnea, sleep disturbances, morning headaches, daytime hypersomnolence) the use of non-invasive ventilation (NIV) is often considered (Miller et al., 1999). The use of NIV has been shown to relieve symptoms of dyspnea, prevent complications such as pneumonia and improve quality

of life (Lechtzin et al., 2002; Hardiman, 2000). The widespread acceptance of non-invasive respiratory aides over the past decade has led to the development of cough-augmentation therapy to improve airway clearance in patients with ALS (Boitano, 2006). An important part of any respiratory management program timing of initiation during the course of a patient's illness. Therefore, clinicians regularly monitor ventilatory function to track decline and stage interventions as indicated.

Assessment of Ventilation

Pulmonary function testing, specifically forced vital capacity (FVC), is the primary means used to assess ventilation and is an integral part of medical management of persons with ALS. Despite differences in the rate of disease progression and site of initial presentation, all patients with ALS exhibit a linear decline in their FVC scores over time (i.e., average decline of 3.5% per month; Fallat, 2002). The overall slope of this decline is the primary clinical indicator of disease progression, predictor of survival (Lechtzin et al., 2002) and the most common trigger for deciding when to initiate non-invasive ventilation and percutaneous endoscopic gastronomy (PEG) tube feedings - crucial aspects of managing the care of patients with ALS.

According to the current Practice Parameters of the American Academy of Neurology (Miller et al., 1999), all patients with ALS should have their FVC routinely measured by spirometry every three months. Frequent measurement is important for timing of therapeutic interventions. Often interventions are indicated when patients are still asymptomatic but their FVC score falls within a critical range of about 50% of the predicted value (Miller et al.).

Although monitoring FVC is essential to anticipating care needs and initiating therapies for symptom management in ALS, the use of FVC as the sole outcome measure of respiratory function is limited by the global nature of the test, the volitional nature of the task, and the physiological demands of performing the FVC maneuver. FVC provides an overall indication of respiratory function based on changes in volume and/or flow as the patient performs a maximal inspiration followed by a maximum expiration. A variety of physiological factors and technical demands contribute to the overall score and it can be difficult to determine the relative contribution of each component of the task. For example, FVC scores are affected by the competency of both inspiratory muscles and expiratory muscles, the compliance of the lung and chest wall, and the ability to coordinate a maximum effort, multi-step task while maintaining a tight lip seal on a mouthpiece. The volitional nature of a task that is dependent on patient coordination and cooperation may complicate interpretation of the data. Specifically, it can be difficult to differentiate sub-maximal patient effort from mild respiratory muscle weakness and/or poor lung and chest wall compliance. As the disease progresses, many patients lose functional use of their upper extremities and require physical assistance to perform FVC. Performance can be further complicated by impaired cognition, difficulty handling thin watery secretions and expectoration of thick, mucus-containing secretions or phlegm during the test. Another limitation of FVC as a sole measure of pulmonary function is its lack of sensitivity to mild weakness of inspiratory or expiratory muscles. In a consensus statement on respiratory muscle testing by the ATS/European Respiratory Society (2002), the authors concluded that

FVC, and other spirometry measures of lung volumes, have poor specificity and sensitivity to mild respiratory weakness. Therefore, it may be necessary to include other tests of pulmonary function to complement results obtained with FVC testing.

Miller et al. (1999) recommend multiple measures of pulmonary function for clinical and research applications, including the use of pressure sensors. Tests involving the use of pressure sensors have been found to be sensitive indicators of respiratory muscle strength and pulmonary function. Trans-diaphragmatic pressure (Pdi) is considered the gold standard measure of diaphragm strength that involves the use of a manometer to collect gastric and esophageal pressures. Although this measure is one of the best predictors of elevated PaCO₂ level and pending respiratory failure (Vitacca et al., 1997; Lyall et al., 2001), it is considered an invasive measure that is unpleasant for most patients and involves sophisticated equipment.

Maximum Inspiration Mouth Pressure (MIP) testing is another option for assessing ventilation. MIP testing is often recommended for patients with relatively normal spirometry measures, but with symptoms of inspiratory weakness and dyspnea (Lechtzin et al., 2002). MIP testing involves inhaling against an occluded airway and measures of less than 60 cm of H₂O pressure have been shown to be associated with disordered sleep breathing and nocturnal de-saturations (David, Bundlie & Mahdavi, 1997) and are sensitive predictors of death within 18 months (Gay et al., 1991). However, in a study of 16 patients with ALS, many participants had difficulty maintaining adequate lip seal on the mouthpiece and the procedure was reportedly uncomfortable for many patients (Fitting et al., 1999).

Sniff Nasal Pressure (SnP) testing is another method of assessing ventilation and may be an optimal secondary outcome measure in addition to FVC testing in research studies. SnP is a relatively new, non-invasive test that provides an indication of diaphragm function and intra-thoracic pressure (Lechtzin et al., 2002). The maneuver involves a short, sharp volitional inspiration by the patient. Pressure is measured with a transducer via a catheter that interfaces with a nasal plug that is inserted into one nostril while the other nostril remains open. The pressure generated while sniffing is hypothesized to reflect alveolar and intrathoracic pressure and is considered an indirect measure of inspiratory muscle strength. Sniff is a simple ballistic maneuver (as opposed to a sustained isometric maneuver as in MIP testing) that allows patients to achieve maximal muscle recruitment of the diaphragm (Nava et al., 1993). Patients with ALS can repeatedly perform the sniff task without failure and normative data are available by age group; height and body mass are not correlated with SnP scores (Uldry & Fitting, 1995).

There are many advantages to SnP testing that make it particularly well-suited for clinical and research purposes. First, addition of the SnP test does not create a significant additional burden to the participants. Testing takes less than a minute and patients find the procedure is natural and easy to perform. Second, SnP is sensitive to even mild changes in inspiratory muscle strength over time. Fitting et al. (1999) found that in 16 patients with ALS, baseline FVC scores were normal (within 10% of predicted values) while SnP scores were 67% and MIP scores were 69% of predicted values. Also, as compared to FVC and MIP testing, Lyall et al. (2001) found that SnP had superior sensitivity and specificity for the presence of hypercapnia (i.e., increased

CO₂ levels in the blood). Third, Fitting et al. also reported that SnP scores showed a linear rate of decline over 18 months (4.2% per month), which makes it a useful measure of change over time in longitudinal therapeutic trials with ALS patients. Fourth, the natural, non-invasive technique of SnP testing may facilitate differentiation of inspiratory muscle weakness from sub-maximal efforts by patients. Nava et al. (1993) found that the level of muscle recruitment by patients with ALS on EMG testing of the diaphragm was more intense in SnP than MIP yet the activity of other muscles of inspiration (i.e., intercostals and sternocleidomastoids) was the same. SnP, therefore, is a more specific test of diaphragmatic function and is important to include in studies of individuals with ALS as the chief cause of respiratory failure is denervation of the diaphragm.

Finally, SnP may be better suited for use in the later stages of ALS when patients have difficulty performing FVC tests. In a longitudinal study of 98 patients with ALS, Morgan et al. (2005) compared the results of FVC testing to MIP and SnP testing. They found that only 86% of participants were able to perform FVC at the final research visit and only 81% could perform MIP testing. However, SnP testing was feasible in 96% of cases. Thus, SnP may be useful in studies in which pulmonary function is an outcome of interest. SnP testing may help to minimize the influence of missing data from patients who cannot perform FVC testing during research trials.

In several studies, researchers have compared SnP testing results to other pulmonary function testing data collected on patients with ALS. Heriter, Rahm, Pausch and Fitting (1994) compared SnP with Esophageal Inspiratory Pressure (Pes) and FVC in 10 individuals with no disease and 12 with neuromuscular and skeletal

conditions. They found that SnP was strongly correlated with Pes in both groups of participants. More recently, Kang, Kim, Ryu, Kim and Yoon (2008) compared SnP, MIP, FVC and peak cough flow data from 28 patients with ALS. SnP was correlated with MIP; SnP and MIP were correlated with FVC; and SnP and MIP were correlated with peak cough flow. Thus, SnP is a clinically feasible, evidence-based technique that is correlated with other pulmonary function measures and is suitable for patients throughout the ALS disease course or those with bulbar onset ALS.

Respiration in ALS: Airway Clearance

Pulmonary hygiene is maintained by clearing the airway of secretions and any foreign materials. Airway clearance of the lower airway is supported by the mucociliary escalator and coughing (Shapiro et al., 1985). The mucociliary escalator lines the tracheobronchial tree and aides in airway clearance by trapping secretions and foreign materials, consolidating them into a cohesive mass of sputum and moving that mass upward to the level of the larynx at the rate of 1-2 centimeters per minute (Shapiro et al.). Coughing is the primary mechanism for clearing retained secretions and any inhaled foreign or aspirated materials up and out of the airway.

Airway clearance function is measured using peak cough flow (PCF). PCF is the maximum expiratory flow produced as the vocal folds open during a cough. Effective PCF is needed to avoid pulmonary complications (Bach, 1993). In healthy adults, PCF is generally greater than 500 L/min (Toussaint, Boitano, Gathot, Steens, & Soudon, 2009; Boezen, Schouten, Potstma & Rijcken, 1994). The current consensus is that a minimum PCF of 160 L/min is required to move mucus from the lungs into the upper airway (Boitano, 2006; Kang & Bach, 2000; McKim, LeBlanc,

Walker, & Liteplo, 2007) and any flow equal to or greater than 180 L/min is considered effective (Toussaint et al.). A PCF of 160 L/min is also the threshold used to determine when tracheal intubation may be indicated (PCF < 160 L/min) or when tracheotomized patients with neuromuscular conditions may be candidates for extubation or de-canualization (PCF > 160 L/min) (Bach & Saporito, 1996).

However, individuals with respiratory weakness and PCF of less than 270 L/min are considered at risk for airway encumbrance (Boitano, 2006) as the mucociliary escalator becomes overwhelmed during respiratory tract infections and the PCF falls below the threshold of 160 L/min (Bach, Ishikawa & Kim, 1997).

Coughing is one of several techniques used to clear the airway. PCF can also be measured during alternative airway clearance behaviours, including forced expiration, throat clearing and hawking. Normative values for PCF during these behaviours are available based on a recent study of 102 adults with typical respiratory function, between the ages of 20 – 85 years (Cleary, Pappachan, Johnston & Chan, 2009) (see Table 1).

Table 1

PCF Values for 102 Adults with Typical Respiratory Function

Age Group	Coughing	Forced	Throat	Hawking
	M (<u>SD</u>)	Expiration	Clearing	M (<u>SD</u>)
		M (<u>SD</u>)	M (<u>SD</u>)	
20-35 (n = 37)	458 (109)	434 (111)	343 (125)	243 (98)
36-50 (n = 18)	504 (139)	490 (159)	415 (134)	272 (111)
51-65 (n = 18)	395 (104)	396 (88)	321 (100)	241 (109)

66-85 (n = 29)	368 (118)	324 (110)	270 (113)	219 (98)
Total (n = 102)	428 (126)	407 (136)	329 (123)	256 (101)

The following section provides a detailed description of cough physiology and cough impairment in ALS. Alternative airway clearance behaviors such as forced expiration, throat clearing, and hawking will also be discussed.

Coughing. Coughing is a complex biomechanical function that consists of three phases: an inspiratory phase, a compressive phase and an expulsion or expiratory phase (McCool, 2006). Coughing can be initiated voluntarily and mediated by the cortex or it can be triggered reflexively at the level of the brainstem by afferent stimuli in the airway (Benditt, 2006).

Volitional coughing begins with active contraction of the diaphragm and recruitment of the accessory muscles of inspiration (i.e., external intercostals, scalenes and sternocleidomastoids) which results in rapid inhalation (West, 2001). The simultaneous contraction of the laryngeal abductor muscles fully opens the true and false vocal folds to minimize airway obstruction and increase the rate of inspiratory airflow (Boitano, 2006). Lung volumes will often reach total lung capacity during this phase. The enhanced expansion of the rib cage lengthens the muscles of expiration, creates tension and increases the potential elastic recoil energy stored within the chest wall (Boitano). Recoil forces are also generated as the contents of the abdomen are compressed by movement of the diaphragm which reaches its maximal downward excursion with these high lung volumes (McKim et al., 2007).

The compression phase of coughing lasts only 0.2 seconds and begins with active adduction of laryngeal muscles which close the true and false vocal fold to trap air within the lower respiratory tract (McKim et al., 2007). Endoscopic evaluations of coughing have shown that the lateral walls of the pharynx move medially to squeeze secretions, food, and fluid out of the pyriform sinuses and position them on the edge of the laryngeal vestibule for clearance out of the upper airway (Murray, 2004). As the diaphragm relaxes, the compressed abdominal contents are released upward. The elastic recoil forces of the expanded lungs causes the chest wall to move inward as the muscles of expiration contract. This contraction compresses the air in the lungs which is trapped by the closed glottis. As intra-thoracic pressure rapidly increases from sub-atmospheric levels to 200-300 cm H₂O, the lower airway is compressed and a large pressure gradient is created between the upper and lower airways (Boitano, 2006).

The expulsion phase occurs when the laryngeal abductor muscles open the glottis and the sub-tracheal air stream is blown outward through an open vocal tract (i.e., mouth open, tongue positioned inferiorly and soft palate closed, directing air through the open oral cavity). The muscles of expiration continue to contract and compress air throughout the lower airway. The high velocity of the expulsive airflow expels mucous and any foreign materials up and out of the lungs. Most normal coughs generate airflow velocities of 360-720 L/min and any peak expiratory flows less than 280 L/min are considered abnormal and associated with increased risk of pneumonia (Boitano, 2006). Pneumonia is an acute inflammatory response within the lungs, bronchial tubes and alveoli that impairs gas exchange and can cause respiratory

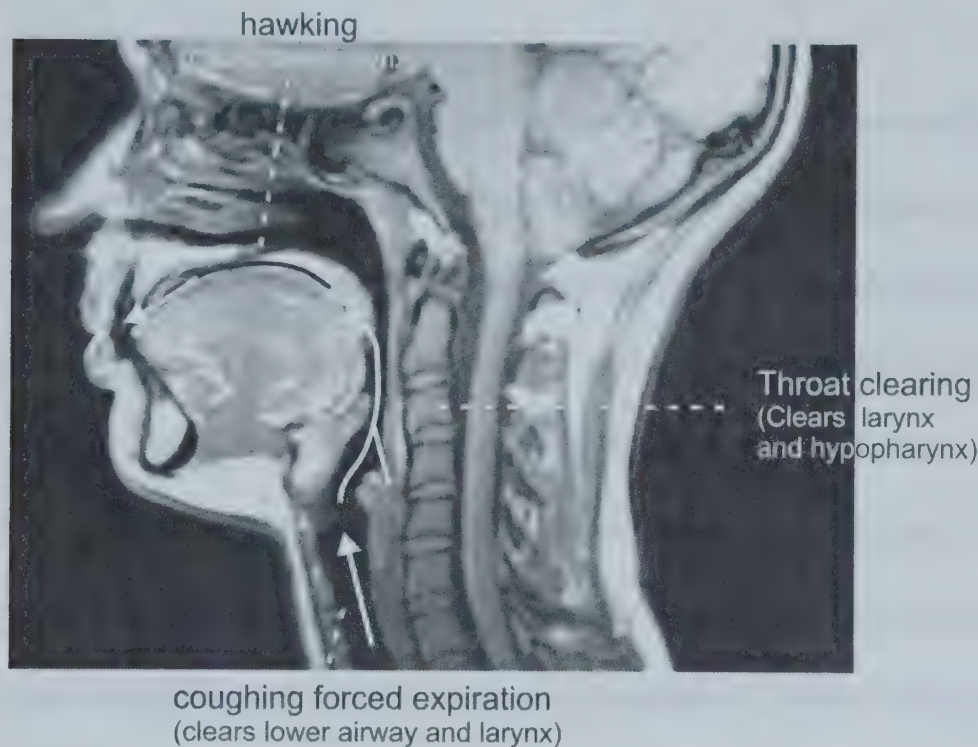
failure (Marik, 2001). Approximately 90% of episodes of respiratory failure in ALS occur concurrent with pneumonia caused by over-production of secretions and the inability to effectively clear the airway (Lahrmann, Wild, Zdrahal, & Grisold, 2003).

Patients with bulbar onset ALS tend to experience cough impairment earlier than those with limb onset, but by the end stages of the disease, neuromuscular involvement affects all phases of coughing (McKim et al., 2007). Loss of phrenic innervation causes diaphragmatic weakness, wasting and paralysis which in turn reduces lung volumes and diminishes the effectiveness of coughing. Laryngeal muscle weakness causes airway obstruction at the level of the glottis during inhalation (Boitano, 2006). Laryngeal involvement also diminishes the ability to seal off the upper airway and impound intrathoracic pressure required to produce a productive cough. Limited chest wall expansion during inspiration reduces the pressure gradient and limits the potential recoil forces stored within the lungs and chest wall (McKim et al.). Weak abdominal muscles and an aberrant pattern of paradoxical breathing may further compromise the dynamic compression of the airway during exhalation phase and reduces velocity of the airflow (Boitano, 2006).

In summary, the ability to generate an effective cough is contingent on many factors. According to McKim et al. (2007), the primary clinical prerequisites for producing an effective cough are a functional glottis, inspiratory volumes greater than 2.3 L, and the ability to generate intra-thoracic pressure greater than 200 cm H₂O.

Other airway clearance behaviours. Although coughing is the primary means of clearing the airway, other behaviours such as forced expiration, throat clearing, and hawking may also be used in conjunction with coughing to expectorate sputum,

secretions, food and fluid from different portions of the upper and lower airways (see Figure 2). Coughing and forced expiration are used to clear the lungs, the trachea, and the larynx of material.



(Adapted from Murray 2002)

Figure 2. Illustration of airway clearance behaviors.

Forced expiration, or huffing, was introduced as an alternative to coughing in chest physiotherapy. Forced expiration involves coughing with and without glottal closure and is used with individuals who have chronic obstructive pulmonary disease (COPD) and cystic fibrosis, conditions in which the central airways are abnormally compliant and may collapse during coughing (McCool & Rosen, 2006). Throat clearing is similar to coughing but involves only closure of the supraglottic or false vocal folds and is effective in expelling material out of the laryngeal vestibule and

into the pharynx (Murray, 2002). Hawking, or horking, involves rapid inhalation followed by contact of the soft palate and the base of the tongue and is used to propel materials from the oropharynx and into the anterior portion of the oral cavity (Murray, 2002).

Endoscopic evaluations of airway clearance in patients with severe bulbar involvement in ALS and other neurological disorders have revealed incomplete vocal fold closure and limited medial movement of the pharyngeal wall which leads to retained secretions within the pyriform sinuses and minimal expulsion of material out of the laryngeal vestibule (Murray & Callaway, 2004).

The inability to clear secretions and debris from the lower airway compromises pulmonary hygiene, causes infection and if left untreated, can lead to hypoventilation and respiratory failure (Perrin et al., 2004). This process results from inflammation and narrowing of the bronchial lumen, which creates resistance to airflow and increases the work of breathing (West, 2001). Ventilation becomes restricted, mucous plugging and atelectasis develop and peripheral airways and alveoli collapse (Ballard, 2002). Secretion clearance is further impaired by immobility that is common during illness, particularly common among patients with ALS. Difficulty clearing secretions in the upper and lower airway can complicate the patient's ability to tolerate NIV treatments (Lahrman et al., 2003) and can lead to significant functional, social, psychological distress and burden on patients, families, and caregivers (Miller et al., 1999).

Respiration in ALS: Airway Protection and Swallowing

Respiration, airway protection and swallowing are integrally related biomechanical functions. Effective airway protection is dependent on the ability to rapidly generate sufficient pressure and flow to move air, food, fluid and secretions at relatively high velocities throughout the aero digestive track. Swallowing and respiration share a common pathway that can be conceptualized as a series of dynamic chambers separated by several sphincters or valves (Murray, 2002). These valves help distribute airflow for respiration, move the bolus during swallowing, and expel (by coughing or other clearance maneuvers) any materials that encumber the airway. These valves must open and close in a synchronized fashion and a tight seal must be achieved to build the pressure needed to facilitate propulsion and provide protection by preventing leakage or spillage before the next chamber is ready to receive it (Murray & Carrau, 2001).

Laryngeal function is the primary interface between respiration and swallowing in maintaining airway protection. The larynx is considered the gatekeeper of the lower airway. It functions as a defense mechanism, a pressure generating valve and a port that can open widely to accommodate improved airflow.

During the pharyngeal phase of swallowing, the larynx moves up and forward to shield the entrance airway from the path of the bolus. Within the larynx, closure of the true and false vocal fold occurs as breathing is stopped to allow the bolus to travel safely through the pharynx. Reflexive inhibition of respiration during swallowing makes it impossible to breathe and swallow at the same time. Laryngeal elevation and closure are maintained throughout a swallowing induced apnea period that lasts

anywhere from 0.3 - 1.0 sec with a 5 ml bolus, 1.0 - 1.9 seconds with saliva or 1 - 20 ml liquid bolus and 3.0 to 7.71 seconds during 100-ml sequential swallows trials (Selley et al., 1989). During this breath-hold interval, the bolus is isolated from the airway as mechanical and pressure-propulsive forces within the pharynx move the material safely into the esophagus. The primary driving force behind bolus propulsion is positive oropharyngeal pressure generated by tongue base retraction and compression against a bulging posterior pharyngeal wall (Martin-Harris, McConnell & McMahon, 2004). At the same time negative hypopharyngeal pressure is generated as the hyolaryngeal mechanism moves up and forward, away from the upper esophageal sphincter and inferior posterior pharyngeal wall (McConnell, 1998). This hyolaryngeal movement creates a mechanical traction effect which pulls open the pharyngoesophageal segment. This segment relaxes immediately prior to laryngeal elevation (Crary & Groher, 2003). This pressure gradient within the pharynx leads to suction and propulsive bolus flow into the upper esophagus. If any of these overlapping patterns of muscle activation becomes disrupted, biomechanical forces are diminished and consequently airway protection and swallowing are compromised.

Any disorder of swallowing is referred to as dysphagia. In individuals with ALS, reduced pressure generation and propulsive bolus flow cause a delay or a misdirection of fluid, food, and secretions as they move from the mouth to the stomach (Crary & Groher, 2003). Up to 80% of all ALS patients experience bulbar involvement as the disease progresses (Yorkston et al., 1995; Traynor et al., 1999). Therefore, most patients with ALS will develop dysphagia at some point in the

disease process; prevalence estimates range from 73% to nearly 100% (Bach, 1996; Wagner-Sonntag et al., 2000).

The clinical presentation of dysphagia in ALS is variable and depends on site and extent of upper and lower motor neuron involvement. Neuromuscular induced weakness and wasting of the lips, face and tongue lead to poor containment of the bolus in the oral cavity, impaired posterior bolus transport, and increased oral residue after swallowing (Kawai et al., 2002). Delayed initiation of the pharyngeal swallow is a common finding in ALS (Ertekin et al., 2000) and causes premature entry of the bolus into the pharynx. As food travels past an open airway into the pharynx before the onset of the pharyngeal swallow, the risk of aspiration and asphyxiation increases. This risk is compounded by delayed and incomplete laryngeal closure, which is a common consequence of bulbar onset of ALS (Bach, 1996). Incomplete hyolaryngeal excursion restricts the duration and extent of cricopharyngeal opening and results in residue in the pyriform sinuses and leads to post-swallowing aspiration (Martin-Harris, 2004). A combination of these specific impairments causes food, fluid or secretions to be retained within the pharynx and/or misdirected into the larynx during swallowing. This places individuals at risk for aspiration pneumonia, airway obstruction, increased fatigue and limited intake during mealtimes. Psychosocial effects include fear, anxiety and distress while eating (Ekberg, Hamdy, Woisard, Wuttge-Hannig & Ortega, 2002; Hadjikoutis, Eccles & Wiles, 2000).

To maintain adequate pulmonary hygiene and prevent infection, the lower respiratory tract must be protected from the introduction of foreign materials.

Aspiration occurs when food, liquid, oropharyngeal secretions, and gastric secretions

pass through the larynx into the lower airway. The extent and severity of the resulting pneumonia depends on the volume, acidity and composition of bacterial or viral pathogens entering the lower respiratory system (Marik, 2001).

Good nutrition is integral to respiratory health (Kasarkis, 2006). Dysphagia often leads to decreased intake, weight loss, malnutrition and dehydration. The consequences of malnutrition include accelerated muscle wasting and fatigue, decreased metabolic rate, weakened immune function resulting in decreased activity levels (Crary & Groher, 2003). Adequate energy intake is necessary to avoid fatigue, replenish glycogen stores and to avoid muscle catabolism (muscle breakdown) for energy (Kasarkis, 2006). Researchers have shown that resting energy expenditure increases as ALS patients near death (i.e., 10% increase in metabolism required to maintain homeostasis; Kasarkis et al., 1996) as a result of the increased effort needed to breathe (Desport, 2001). Ensuring safe swallowing and adequate nutrition by mouth for as long as possible is a key component of end-of-life care for patients with ALS.

Another common consequence of dysphagia, and a significant problem for individuals with ALS, is sialorrhea. Sialorrhea is characterized by poor oral containment of thin secretions resulting in anterior spillage out of the mouth (drooling) and posterior spillage into the pharynx (Andersen, Gronberg, Franzen & Funegard, 2001). Secretions can encumber the upper airway and cause discomfort, nausea, coughing, gagging, a choking sensation and even aspiration in certain cases (Andersen, et al.). In a retrospective study of 69 individuals with dysphagia (including an unspecified number of hospitalized participants with ALS), Murray,

Langmore, Ginsberg, and Dotsie (1996) used fiberoptic endoscopic techniques to visualize and quantify the amount of secretions retained with the oropharynx after swallowing. Participants with visible oropharyngeal secretions after swallowing were seven times more likely to aspirate than those without retained secretions in the pharynx. Secretion management problems are exacerbated by the presence of thick secretions which can develop secondary to dehydration and decreased cough effectiveness (Miller et al., 1999), both of which are common in individuals with ALS and dysphagia.

In addition to health and safety concerns related to sialorrhea, patients with ALS and their families report that sialorrhea has functional and psychological and social consequences. The functional burdens include constant changing of clothes and linen; skin irritations, foul smelling odor, impaired use of augmentative and alternative communication devices, particularly electronic devices (Borg & Hirst, 1998). Psychological distress includes embarrassment, which may lead to social burdens (e.g., withdrawal and social isolation). Anecdotal reports suggest that patients with sialorrhea avoid eating with others because of drooling and frequent coughing episodes at mealtimes (Cleary, Kalra, & Johnston, 2007).

Sialorrhea is often assessed using patient self-rating scales and proxy measures of severity of the problem (e.g., number of times clothes are changed in a specific time period). Management of sialorrhea is dictated by the nature and severity of the problem. Miller et al. (1999) recommend a combination of approaches including pharmacological therapy, the use of suction machines and cough augmentation techniques to help clear the airway. These strategies may be used in

conjunction with other strategies to improve swallowing function and minimize aspiration risk.

Generally, dysphagia in ALS is managed using myriad compensatory techniques to decrease the likelihood of aspiration while maintaining adequate nutrition and hydration. Although the pharyngeal stage of swallowing was once considered an invariant, brainstem-controlled reflex, some events within this stage (vocal fold closure and laryngeal elevation) may be modified through volitional control (Robbins, 2006). One such technique, the supraglottic swallow, is recommended to improve laryngeal closure and airway protection in patients with ALS (Wagner-Sonntag et al., 2000). This maneuver involves a volitional pre-swallow breath hold, a forceful cough after the swallow and a second ‘dry’ swallow to clear any residue in the airway. This supraglottic swallow is designed to achieve volitional vocal fold closure before and during the swallow by causing the arytenoid cartilages to tilt anteriorly towards the base of the epiglottis (Logemann, 1988; Wheeler-Hegland, et al., 2009). The mechanisms underlying the supraglottic swallow, as well as its effectiveness in protecting the airway from aspiration, have been studied in individuals with normal swallowing function (Bulow, Olsson & Ekberg, 1999; Donzelli & Brady, 2004) and in those with dysphagia (Bulow et al., 2001; Logemann & Kahrilas, 1990) with positive results (i.e., increased extent and duration of laryngeal closure, improved tongue base retraction, increased intrabolus pressure during the swallow). Individuals with ALS often have spared sensation in the pharynx and are able to sense retained material that needs to be cleared. Therefore, the

supraglottic swallow may be particularly well-suited as a technique to help clear the airway of food, fluids or other materials.

Individuals with respiratory insufficiency may also be at more risk for aspiration because they simply can't keep their airway closed long enough to let the bolus clear the pharynx. In cases of ALS swallowing is often compromised by an aberrant pattern of inhalation after swallowing instead of exhalation, which increases the likelihood of aspiration and choking (Hadjikoutis, Pickersgill, Dawson, & Wiles, 2000; Borasio, Voltz and Miller, 2001). The supraglottic swallow technique prevents this abnormal respiratory phase pattern during swallowing by promoting more conscious control over respiration during swallowing. Individuals are taught to take large pre-swallow breath-hold which may enable them to withstand a prolonged swallowing apnea period and allow more time for materials retained within the pharynx to be cleared by gravity. The relatively large volume of trapped air may also facilitate a stronger post-swallow cough and ensure a more normal pattern of post-swallow expiration.

Framework for Respiratory and Swallowing Interventions in ALS

In the recent past, the prevailing message in the clinical management of individuals with ALS was to avoid taxing patients with any intervention that involved exertion of effort (Kang, 2006). Palliative approaches to care were favoured over interventions that required active and sustained participation by patients (Borasio, 2001). A similar situation existed for patients with Alzheimer disease, with most care directed towards comfort and safety, rather than maximizing remaining functional abilities (Bayles et al., 2001). Teaching patients to use volitional airway clearance

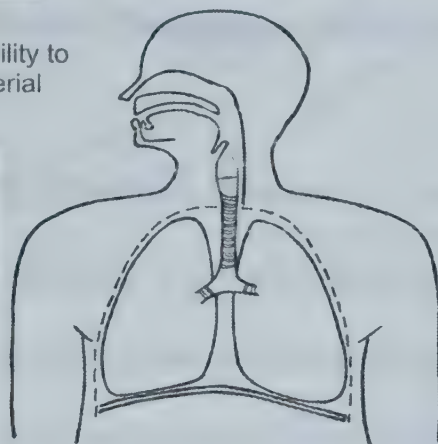
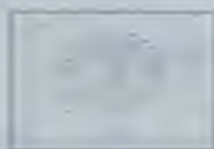
maneuvers and compensatory swallowing strategies such as the supraglottic swallow are consistent with a strength-based approach to rehabilitation for individuals with ALS. Strength-based approaches involve capitalizing on relatively spared functions or abilities to support more impaired functions (Bayles & Tomoeda, 1997). Patients with ALS often retain the following respiratory and swallowing-related abilities: (1)

Pharyngeal sensation: The ability to sense retained material in the pharynx provides a cue for the patient to initiate airway clearance maneuvers and judge the effectiveness of these maneuvers in clearing material from the airway; (2) Spared mucociliary escalator function: In ALS, the mucociliary escalator is not affected by the disease process. The mucociliary escalator aids the movement of substances up through the pharynx. Thus, implementation of airway clearance maneuvers and safe swallowing strategies is aided by intact physiology; (3) Ability to learn: Although many patients with ALS have cognitive dysfunction (Woolley & Katz, 2008) this impairment does not automatically preclude their ability to benefit from awareness training and practice with new breathing and swallowing procedures. Interventions that build upon these strengths should be designed as part of a comprehensive treatment program that focuses on respiratory function, per se. Currently, the foundation of such programs is the provision of cough augmentation therapy, most commonly known as lung volume recruitment.

Maximize volitional use of airway protection and clearance strategies



Capitalize on the ability to sense retained material



Support spared mucociliary escalator function

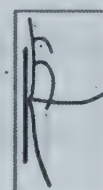


Figure 3. Strength-based rehabilitation in ALS.

Lung Volume Recruitment

LVR is a cough augmentation technique used to help patients clear mucous and secretions up and out of the lungs (McKim et al., 2007; Miller et al., 1999). Cough augmentation therapy can be applied mechanically via a ventilator or manually without sophisticated equipment. LVR is a manual breath stacking technique that allows patients to maximize the volume of air they can inhale. A resuscitator bag equipped with a one-way-valve and a mouthpiece is compressed in a series of breath-stacking maneuvers until the patient reaches their maximum insufflation capacity (MIC) (McKim et al., 2007). To accommodate the larger lung volume, the distended lung and chest wall become more compliant over time (Grippi, Litzky & Manaker, 2001). Improved lung compliance has been estimated by measuring the difference between MIC and unassisted vital capacity and PCF

immediately before and after the treatment is given (Boitano, 1996). Upon maximal insufflation the patient produces an augmented cough and the difference between these two values is one index that researchers have used to judge the effectiveness of manual and mechanical cough augmentation interventions (Toussaint et al., 2009; Trebbia, 2005).

A typical LVR session involves 3 – 5 trials of manual insufflation coupled with augmented coughing. LVR allows patients to generate sufficient force to clear excessive mucous and retained secretions from their lungs either during the treatment session or over the course of the next few hours. In ALS clinics where the LVR technique is frequently used, many patients have anecdotally reported improved spontaneous cough efforts and the sensation of a cleared airway for several hours after each LVR treatment session (McKim et al, 2007; Cleary, Wheeler, Kendall, Kalra, & Johnston, 2008).

Potential LVR treatment mechanisms. LVR is hypothesized to increase lung volumes and improve coughing effectiveness by an interaction of related biomechanical events including : recruiting collapsed lung segments, improving compliance and range of motion of the lung and chest wall, (McKim et al, 2007) and eliminating flow limitation or choke points within the lower airway. The goal of LVR is to, literally, ‘recruit’ lung volume.

In restrictive lung disease, like ALS, neuromuscular changes in the diaphragm lead to less forceful contraction, decreased range of motion and reduced intra-thoracic pressure generation. As the lung and chest wall become stiff and less compliant over time, lung volumes decline to the point where the mechanical tethering effect of the

stretched alveoli is lost at lower lung volumes and the distal airways are not held open. Choke points are created within the airways as the bronchi become more constricted, increasing resistance to airflow. These flow limitations lead to reduced peak flow rates and subsequent further retention of secretions. Distal lung segments also tend to close off at low lung volumes further complicating secretion clearance and restricting the volume of air exchanged with each breath. As the disease progresses, the unassisted cough increasingly lacks sufficient force to shear secretions, mucus and foreign debris off the inner wall of the bronchi (Boitano, 2006), to clear the larynx and the lateral walls of the pharynx, and to expectorate material out of the airway.

The goals of LVR are to periodically hyper-insufflate the respiratory system, to stretch the lung and chest wall such that the patient is able to increase cough flows and increase the volume of air recruited with each breath (see Figure 4). Increased volume is achieved by stretching the lung and chest wall and facilitating more elastic recoil force and contractile force. At high lung volumes the alveoli are distended and choke points do not occur because the mechanical tethering of the stretched alveoli creates elastic tension that allows the bronchi to remain open. The increased cross-section of the airway leads to reduced airway resistance to airflow which translates to improved lung volumes, higher peak cough flows and improved airway clearance.

The hypothesized mechanisms of improvement in lung volumes after LVR are based on empirical research findings. In a recent case study, lung volumes were measured before and after LVR, the patient demonstrated a 7% increase in FVC (and a 5% increase in FEV1) immediately after the treatment and she reported feeling

“stretched out.” The respiratory therapist performed auscultation of the patient’s lungs during the first trials of LVR and reported “snapping and crackling sounds” as the patient reached maximal insufflation capacity. These sounds were attributed to the action of closed alveoli and distal lung segments being pulled open and aerated (see Figure 5).

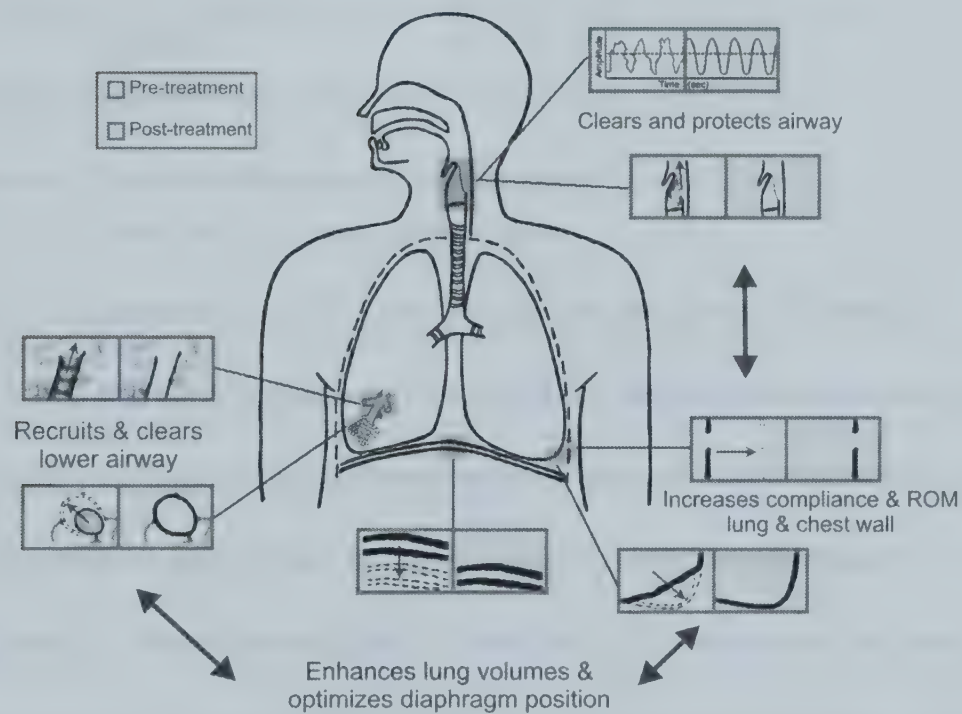


Figure 4. Hypothesized treatment mechanisms in LVR.

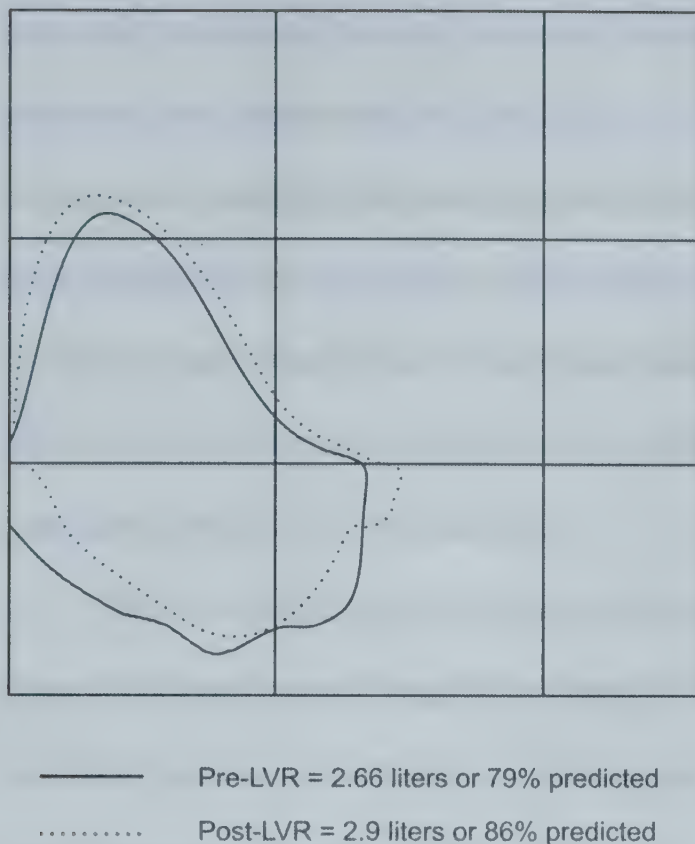


Figure 5. Example of an FVC flow loop before and after LVR training.

The finding of volume improvement for this patient immediately after LVR is consistent with a growing number of reports. Bach (1993) used manual breath stacking with 13 participants with mixed neuromuscular etiologies who were also long term NIV users (average age 45 years and a 15 year history of using NIV approximately 21 hours per day). Manual breath stacking was used with these patients over five trials and was shown to increase PCF by 22% or .43 L/min and improve MIC by an average of 218% or 1.07 liters immediately after the treatment (time interval unspecified by authors). In eight patients, the unassisted FVC returned to baseline level after the manual insufflation. However in five participants FVC increased by an average of 29% or 138 ml.

In a study of 14 children with muscular dystrophy, Schwake, Mellies, Ragette, Voit & Teschler (2003) reported an immediate and robust effect in PCF and MIC

after only two days of training in manually assisted insufflation. Participants improved their spontaneous PCF by 78% or .87 L/min and MIC by 68% or .39 L on average over baseline in the best of three trials immediately after the therapy with no adverse side effects noted. These authors also provided pre and post-treatment chest x-rays to support results from a single case study of atelectasis in a 14 year old boy who recovered in five days using manual insufflation and assisted coughing treatments administered 10 times/day.

Only two published studies have included participants with ALS. Kang and Bach (2000) conducted a longitudinal study of 43 patients with mixed etiologies related to neuromuscular disease (including nine participants with ALS). These participants were prescribed 10 – 15 maximal lung insufflations by manual air-stacking each day and were followed for 3 – 6 months. Follow up assessments (at an unspecified time point between 3 – 6 months) showed that 30/43 participants (6/9 with ALS) had increased their FVC and pulmonary compliance (as measured by MIC) over their baseline by an average of .49 L or 55%. The remaining 13 participants had decreasing values. The 30 participants with improved MIC also demonstrated 16% (or .6 L/min) increase in assisted PCF over time, their spontaneous PCF decreased by 4%. One of the primary limitations of this study is the lack of procedural specificity; that is, the participants were responsible for conducting their own manual insufflation and the researchers had to rely on self-report to ensure that the treatment was carried out as prescribed.

In a retrospective study, Tzeng and Bach (2000) examined rates of acute respiratory illness, frequency of hospital admission and inpatient length of stay for

two groups of participants with mixed etiologies who were on NIV ($n = 94$, six patients with ALS). One group started manual breath stacking via LVR, manual cough assistance (i.e., abdominal thrust) and mechanical insufflation-exsufflation cough assistance when their PCF levels fell below 270 L/min or their FVC fell below 2 L. The other group received these interventions only intermittently after episodes of pneumonia or acute respiratory infections. Tzeng and Bach reported that the group of participants who had earlier and more intensive use of a combination of non-invasive respiratory aides had a significantly lower rate of hospitalization, fewer days hospitalized, and a lower rate of intubations during hospital admissions for respiratory failure. The authors used a between groups paired t tests to longitudinally compare the outcomes of the two respiratory treatment protocols. However, given the multiple treatment interactions within each group, it is difficult to discern the relative contribution of LVR to reported health outcomes.

Based on these studies and anecdotal reports, LVR is associated with positive outcomes related to improved cough effectiveness as measured by PCF in augmented coughing and spontaneous coughing immediately following treatment and improved ventilation as measured by MIC. However, methodological concerns make it difficult to interpret some of the study findings. Researchers used relatively weak research designs without concurrent controls, on small sample sizes with poorly described participants who simultaneously received multiple respiratory interventions according to unspecified treatment protocols.

In addition to these concerns, many issues remain to be addressed in future studies of LVR. First, the effects of LVR for patients with ALS remain speculative.

Few of the study participants had ALS (fewer than 22 in total, across studies) and thus it is unclear how these findings relate specifically to the management of patients with ALS. Second, many questions regarding treatment effects remain unanswered, including intensity and duration of the effect on spontaneous coughing, generalization of the treatment effect to other airway clearance behaviors, the potential impact this effect may have on airway protection and compensatory swallowing maneuvers and other factors that affect patient responsiveness to this treatment.

Despite limited research evidence on the use of manual insufflation via LVR, this technique is considered standard practice at many ALS clinics in Canada. Controlled research experiments are necessary to support the use of these clinical techniques and develop optimal practice parameters for the care of patients with ALS.

Pilot Study

Prior to conducting the thesis project, we tested the feasibility of the procedures in a pilot study (Cleary, Wheeler, Kalra, & Johnston, 2007). Participants were eight individuals with degenerative motor neuron disease (seven with ALS, one with progressive lower motor neuron syndrome) who were doing LVR at the time of the study. A one group, pre-post test design (O X O O) was used. PCF and FVC were measured at four time points: before, during, 15 and 30 minutes after LVR. PCF was measured during coughing and alternative airway clearance maneuvers. Participant perspectives on LVR and its effects were solicited using semi-structured interview questions.

PCF results. As a group, participants showed improvement on all cough and airway clearance measures from baseline to 30 minutes post treatment.

Table 2

Mean PCF (L/min) During Airway Clearance Maneuvers (n = 8)

	Baseline	Post	Post	Post
		Treatment	Treatment	Treatment
		(> 5 min)	(15 min)	(30 min)
Spontaneous cough	215	291	274	272
Post swallow (Ps)	193	273	241	250
cough				
PS forced expiration	136	143	166	165
PS throat clearing	84	145	125	145
PS hawking	44	105	112	108
Supraglottic swallow	167	269	249	262

Although these results are positive, individual variation did exist with some participants exhibiting declines in PCF values from baseline to 30 minutes post-treatment. Specifically, two participants showed a decrease of 5 – 10 % in PCF values from time 1 to time 4.

FVC results. Results are reported for seven participants as one participant was unable to use the Spirometer). In general, FVC increased immediately after an LVR trial but decreased to baseline levels at 15 minutes and below baseline levels after 30 minutes. Similar to PCF results, some individual variability existed: two participants showed a slight increase in FVC from baseline to 30 minutes.

Table 3

Mean FVC Results (n = 7)

	Baseline	During LVR	Post LVR (15 minutes)	Post LVR (30 minutes)
L/min	2.18	3.19	2.20	2.10

Participant perspectives on LVR. The majority of the participants agreed that LVR had a positive effect on their functional status and quality of life, it helped them clear their secretions and it reduced their anxiety about breathing. Participants were less certain that LVR decreased their anxiety regarding secretion management specifically. Perspectives were captured in participant quotes as well as on a Likert-type scale, which was modified (shortened) for use in the current study.

Discussion of pilot study results. Preliminary findings of the effects of LVR on measures of vital capacity and peak cough flows during airway clearance techniques were positive and provided the foundation for the thesis study. First, we confirmed that the proposed thesis study was feasible. Although one participant was unable to use the spirometer, the others had no difficulty completing the protocol. All participants reported feeling fatigued at some point during assessment and treatment sessions. Therefore, in the thesis study, we ensured adequate rest breaks within the protocol and made efforts to schedule data collection sessions at the time of the day when each participant was least tired. Second, the pilot data were used in a power analysis to determine the optimal sample size for the thesis study. Third, minor

modifications were made to the protocol to improve the proposed study: an additional measure of respiration (SnP) was added to the protocol and a high range peak cough flow meter with a mask was used after two participants in the pilot produced maximum readings on the lower flow meter.

Purpose of the Study

The purpose of this study was to evaluate the effects of LVR on respiratory function and swallowing in patients with ALS. Also of interest were the perspectives of participants regarding LVR. The current rationale for doing LVR is to clear secretions, however, further benefits may be realized if LVR facilitates safe swallowing. An important purpose of determining the duration of the treatment effect is the potential benefit of performing the treatment prior to meals and determining if this treatment has a protective effect over the length of a typical meal (i.e., 30 minutes).

Research Questions

- (1) What is the intensity and duration of the LVR treatment effect on standard tests of pulmonary function?
- (2) What is the effect of LVR on volitional airway clearance behaviours (i.e., hawking, throat clearing, coughing and forced expiration) that would have a protective effect during swallowing and eating?
- (3) What is the effect of LVR on performance of a compensatory safe swallowing technique, specifically the supraglottic swallow maneuver?
- (4) What are the participants' perspectives regarding the effects of LVR on their breathing and secretion management?

Methods

Participants

The study was approved by the Health Research Ethics Board at the University of Alberta, with additional approvals from Caritas Health and Alberta Health Services. Participants were recruited through the University of Alberta Hospital (UAH) ALS Clinic and the Misericordia Hospital using approved recruitment procedures. Clinic patients with ALS were made aware of the study and asked if they were interested in being contacted by the principal investigator.

To participate, individuals met the following inclusion criteria:

1. Were diagnosed with ALS according to *The Revised El Escorial* criteria (Brooks et al., 2000) and were receiving services through the University of Alberta Hospital's ALS clinic, or the Calgary ALS clinic at the University of Calgary Medical Clinic.
2. Were fluent in English and able to provide informed consent.
3. Were presenting with significant respiratory dysfunction (as measured by *The Revised ALS Functional Rating Scale* (ALSFRS-R) (Cedarbaum et al., 1999) during routine clinic visits to the ALS clinic.
4. Were participating in LVR therapy provided by respiratory therapists at the University of Alberta Hospital ALS clinic at the Misericordia Community Hospital and were using the LVR equipment at home (for a minimum of two weeks prior to the study). (See Appendix A for the

treatment algorithm used by clinic staff to determine candidacy for LVR treatment.).

5. Were able to take some food and liquid by mouth (could be meeting nutritional needs via PEG tube).
6. Were able to communicate using speech, handwriting or voice output communication aid to make basic needs known.

A power analysis was conducted to help determine an adequate sample size for the study. Effect size data were based on pilot study findings in which participants had a mean PCF increase of 57 L/min from baseline to 30 minutes ($d' = .66$) where $d' = \frac{M_1 - M_2}{s}$, where M is the mean for each of the two test conditions, and s is the standard deviation (pooled). Using a power table (Cohen, 1988) and guidelines specific to a repeated measures design (Portney & Watkins, 2000), with a one-tailed test at the 0.05 level ($\alpha = .05$), an effect size of .66 and a power of .80, it was estimated that 28 participants would be necessary to detect the presence of a significant difference between treatment conditions.

Thirty-four participants with ALS were recruited to participate in the study. However, two individuals were unable to complete the treatment protocol because of concomitant health issues: one participant had cognitive and visual impairments that precluded his ability to follow directions during sessions, the other participant's peak cough flow rate was below the minimal threshold of the PCF meter (less than 30 L/min) and she was considered too medically fragile to complete the study. The other three individuals did not meet inclusion criteria for participation (i.e., were not consistently using LVR).

The final study sample consisted of 29 participants, 13 women and 16 men, ranging in age from 35 to 86 years ($M = 65.4$ years, $SD = 11.5$) (see Tables 4 and 5 for sample characteristics). Six participants (20.7%) had the bulbar onset form of ALS, 22 had the limb onset form (75.9%) and one participant had respiratory onset ALS. Participants' mean length of time from diagnosis to initiating LVR therapy was 21.3 months (ranging from 0 to 72 months; one participant started LVR on the day she received her diagnosis). At the time of the study, participants had been doing LVR therapy for an average of 4.8 months ($SD = 7.01$) ranging from 0.5 to 32 months.

Several measures were used to estimate disease severity of the study participants. First, scores on the *Revised ALS Functional Rating Scale (ALSFRS-R*; Cedarbaum et al., 1999) were used. The ALSFRS-R is a questionnaire-based scale that measures a patient's ability to carrying out activities of daily living. The scale is used extensively with patients with ALS for clinical and research purposes. The measure yields quantitative scores on Likert scales that are used to monitor the progression of a patient's disability. In the current study, this scale was only administered if a recent score was unavailable from the participant's chart. The median ALSFRS-R score for the study sample was 29.3 ranging from 14 to 41 out of a total possible score of 48. Bulbar sub-scores of the ALSFRS-R also were calculated to characterize the overall degree of participants' speech, salivation and swallowing impairment. The median ALSFRS-R sub-score was 9.1 ranging from 4 – 12 out of a possible score of 12 for this sub-section.

Second, baseline FVC was compared to predicted normal values. Participants’ FVC ranged from 23 – 93% of predicted normal values (M = 58%, SD = 21.9) based on gender, age, height, and ethnic origin (Knudson, Slatin, Lewowitz & Burrows, 1976). As a third estimate of severity of disease, average PCF rate was also compared to predicted normal values (Cleary et al., 2009). Mean PCF rate was 245 L/min or 62% of predicted normal values based on gender, age, height, and ethnic origin. Finally, the number of participants using non-invasive ventilation (NIV) and frequency of use were reported. The use of NIV is typically associated with increased disease severity (Miller et al., 1999). In the current study, 10 participants reported using NIV intermittently 2 – 4 hours per day for an average of 6.8 months. In summary, the majority of participants were moderately impaired in terms of disease severity based on these measures, and were characterized as having mild respiratory insufficiency and early bulbar symptoms at the time of the study.

Table 4

Sample Characteristics: Demographic Information

ID	Age	El Escorial Diagnosis	Site of onset	Time post diagnosis (Months)	LVR Duration (Months)
1	58	Probable	Bulbar	0.1	0.9
2	68	Probable	Bulbar	2.4	1.5

3	35	Probable	Limb	72.1	17.9
4	69	Definite	Limb	36.5	9.4
5	83	Probable	Limb	33.4	15.5
6	60	Probable	Limb	51.9	0.7
7	71	Probable	Respiratory	5.8	3.9
8	70	Probable	Bulbar	4.2	1.0
9	72	Definite	Limb	1.7	1.7
10	52	Probable	Limb	52.2	31.9
11	65	Probable	Bulbar	10.3	1.0
12	67	Probable	Limb	14.5	9.9
13	57	Probable	Limb	32.1	3.1
14	74	Probable	Limb	9.8	1.3
15	48	Probable	Limb	19.4	0.4
16	60	Definite	Limb	2.6	1.8
17	51	Definite	Limb	18.0	11.4
18	53	Probable	Limb	65.8	2.4
19	82	Probable	Limb	7.4	3.9
20	67	Probable	Limb	1.6	0.5
21	65	Probable	Bulbar	7.2	0.5
22	58	Probable	Limb	49.2	1.5
23	74	Probable	Limb	17.8	0.4
24	77	Probable	Limb	16.2	4.1
25	63	Probable	Limb	6.3	.9
26	59	Probable	Limb	16.7	7.7
27	78	Probable	Bulbar	7.2	2.8

28	86	Probable	Limb	18.0	0.9
29	61	Probable	Limb	28.3	0.3

Table 5

Sample Characteristics: Functional Status

ID	FVC (% predicted)	PCF (% predicted)	ALSFRS-R Total Score	ALSFRS-R Bulbar scores	NIV Duration (months)
1	52.1	40	39	2/0/2=4	-
2	23.1	37	25	2/1/2=5	-
3	66.5	76	32	4/3/4=11	25.0
4	87.2	101	38	3/4/4=11	-
5	30.8	68	35	4/4/4=12	-
6	46.6	40	24	3/4/4=11	0.7
7	30.1	33	31	3/3/4=10	6.9
8	54.7	69	38	2/1/2=5	1.0
9	66.1	81	38	3/4/4=11	-
10	48.6	48	23	4/4/4=12	-
11	64.7	44	27	3/0/2=5	1.8
12	41.0	66	27	3/4/4=11	11.5
13	61.8	76	14	3/2/2=7	-
14	92.7	95	29	4/4/4=12	-
15	42.3	26	21	3/4/4=11	-

16	47.9	76	35	3/4/4=11	1.4
17	48.5	54	41	4/3/4=11	-
18	76.3	167	28	3/2/3=8	-
19	41.5	32	31	2/2/3=7	-
20	85.0	64	26	3/4/4=11	-
21	50.6	35	40	0/2/2=4	-
22	64.7	101	25	3/4/3=10	0.3
23	52.2	34	27	3/4/3=10	-
24	58.3	46	22	3/2/4=9	-
25	62.6	46	21	3/4/3=10	12.0
26	46.6	76	35	4/4/4=12	7.7
27	63.9	54	28	2/2/1=5	-
28	128.6	84	32	3/4/3=10	-
29	48.3	58	21	3/4/3=10	-

To further characterize participants' speech, swallowing and secretion management ability, the SWAL-QOL/Care scale (McHorney, et al., 2006) was used. The SWAL-QOL is a 44-item questionnaire that has been clinically validated and is used to assess patient perspectives on mealtime related quality of life across ten domains including: Burden; Eating Duration; Eating Desire; Symptom Frequency; Food Selection; Communication; Fear; Mental Health; Social; Fatigue; and Sleep. Administration of the entire scale yields a Total scale score and three Symptom Severity sub-scale scores (i.e., oral symptoms, pharyngeal symptoms, saliva symptoms), which can be used to differentiate normal swallowing from dysphagia (See Tables 6 and 7).

As a group, the participants rated their general psychological burden associated with dysphagia as mild to moderate and they indicated a relatively strong desire to continue to eat. They reported mild difficulty with the oral stage of swallowing, with only intermittent problems with excessive saliva or food sticking in the mouth while eating. Pharyngeal symptoms during mealtimes had slightly more impact and they reported occasional coughing and throat clearing during meals with intermittent choking. Fatigue, poor sleep, and prolonged meal duration were the domains most affected and were judged as having a moderate impact on the quality of the mealtime experience.

Participant perspectives on swallowing and secretion management were consistent with their healthcare provider's assessment of function on the ALSFRS-R. A median ALSFRS-R rating of 3 related to swallowing indicates that the group as a whole still had a relatively safe swallowing for most foods and a low risk of aspiration. At this stage, minor diet modifications may be indicated (e.g., avoiding nuts, hard candies, dry meat). A median ALSFRS-R rating of 3 on salivation signifies slight difficulty handling thin, watery secretions, some nighttime drooling and minimal issues with thick mucus-containing salivary secretions and/or phlegm. Pharmacological approaches are typically discussed but not routinely initiated at this point in the disease process.

Table 6

SWAL-QOL Quality of Life Concept Scale Ratings

Quality of Life	Mean (/100)	Standard Deviation
Concept Scales		

General Burden	70.5	24.8
Food Selection	71.8	27.4
Eating Duration	61.6	32.9
Fear of Eating	65.1	22.0
Sleep	57.3	21.9
Fatigue	47.4	16.5
Communication	64.1	29.36
Mental Health	72.6	23.9
Social Function	69.3	30.9
Eating Desire	75.6	35.6

*SWAL-Qual Quality of Life Concept Scales reported on a 0 to 100 metric; 100 indicating most favorable state, 0 the least, scores in between representing % of total possible score achieved

Table 7
SWAL-QOL Symptom Severity Scale Ratings

Scales	Mean	Standard Deviation
Pharyngeal Symptoms	26.2	5.8
Saliva Symptoms	6.6	2.1
Oral Symptoms	12.2	3.5

Notes: Pharyngeal symptoms scale: 7-item factor (highest possible score 35);
Saliva symptoms scale: 2-item factor (highest possible score 10); Oral symptoms
scale: 3-item factor on (highest possible score 15)

The vast majority of participants were living at home at that time of the study ($n = 26$). Two were living in long-term care facilities and one individual was in hospital when the data were collected. Most participants lived in urban settings ($n = 21$) in Alberta (see Figure 6).



Figure 6. Geographic distribution of participants in Alberta.

Research Design

A repeated measures cross-over research design was used to examine the effects of LVR on pulmonary, respiratory and swallowing ability. In this design, all participants receive both treatments in sequence, eliminating the need for a separate comparison group that does not receive the treatment. The order of the treatments was counterbalanced to control for order effects that may occur when one treatment always precedes the other (Portney & Watkins, 2000). In this study, half of the

participants received the LVR treatment followed by the no treatment/control condition and half participated in the no treatment/control followed by the treatment condition (see Tables 8 and 9 in the *Procedures* section). The cross-over research design is appropriate when treatment effects are rapid and reversible (i.e., expected to return to baseline within 24 hours). LVR was not expected to have significant cumulative effects, based on findings reported in previous studies and clinical reports. However, participants were asked to refrain from LVR for 24 hours prior to each research session to ensure a sufficient ‘washout period’ for potential treatment effects to disappear.

The use of the cross-over design is also considered appropriate for this thesis project, which is a Phase II treatment outcomes study. Robey & Schulz (1998) adapted a five-phase model for structuring clinical outcomes research, based on work by oncologists Greenwald and Cullen (1985). In Phase I, the goal is to develop critical hypotheses for later testing, to establish the safety of a treatment and to determine whether the treatment is active. In this phase, single-subject experimental designs, case studies, small single group pre-post studies and retrospective studies are appropriate. If the results of Phase I indicate testing the efficacy of the treatment, then a Phase II study is undertaken.

In Phase II, the objectives are to formulate and standardize protocols and methods, explore the dimensions of the treatment effect (e.g., magnitude, duration) and to develop an explanation as to why the treatment works. In Phase II, small group experimental studies are considered appropriate and participants should be sampled

only from the target population for whom the treatment is intended (Robey & Schulz, 1998).

In preparation for the thesis study, a Phase I pilot study was conducted using a single group, pre-post LVR treatment ($n = 8$) (Cleary et al., 2007). Preliminary findings of the effects of LVR on measures of vital capacity and peak cough flows during airway clearance and protection while swallowing were positive. The results of this Phase I pilot study suggested that a therapeutic effect was present and that LVR may offer increased airway protection if done prior to eating. This thesis project represents a specific step in a line of studies on clinical outcomes of LVR for patients with ALS. Using a quasi-experimental group design at this stage is consistent with accepted models of clinical outcomes research.

Procedures

Each participant completed one treatment session and one control session, separated by a minimum of 24 hours. In the treatment session, participants were instructed to perform LVR as they typically would, with breaks between trials to allow for data collection (see Table 8). Data were collected on pulmonary, respiratory and swallowing function at three time points: at baseline/prior to performing LVR (time 1), immediately after performing LVR (time 2) and 30 minutes after LVR (time 3). Each participant performed a typical LVR session (i.e., five maximal insufflations with two trials augmented coughing - MIC). Participants were assisted with set-up if necessary; however, they performed LVR independently. In the control session, the protocol was the same except that no LVR treatment was performed. Data were collected at the same time intervals (Table 8).

Table 8

Protocol for Treatment and Control Session Data Collection

Baseline	Treatment (X) or Control	Post-treatment
assessment (O ¹)	Session and post- treatment assessment (O ²) – 15 minutes	assessment (O ³) – 30 minutes
PCF: unassisted cough	Treatment Session: LVR 1, 2 PCF at MIC LVR 3, 4, 5: FVC at MIC Control Session: Self- report questionnaires, SWAL-QOL, ALSFRS-R	PCF: unassisted cough
PCF: forced expiration, throat clearing, hawking	PCF: unassisted cough	PCF: forced expiration, throat clearing, hawking
PCF: supraglottic swallow (10 cc H ₂ O)	PCF: forced expiration, throat clearing, hawking:	PCF: supraglottic swallow (10 cc H ₂ O)
SnP	PCF: supraglottic swallow (10 cc H ₂ O)	SnP
FVC	SnP	FVC
	FVC	
Total: 23-29 trials	Total: 27-34 trials	Total: 23-29 trials

Note: Each PCF task and FVC performed with 3-5 trials; SnP performed with 10 trials

Instrumentation and Measures

- 1) Forced Vital Capacity (FVC) – Forced vital capacity (FVC) is the primary outcome measure used to judge prognosis and to guide most therapeutic interventions. FVC is defined as the maximum volume of air that can be exhaled with forced effort following a maximal inspiration (College of Physicians and Surgeons of Alberta, 2004) and is measured using spirometry. Using a Wright Mark 14 hand-held spirometer, the following measures were obtained:
 - a. Maximum volume of Forced Expiratory Flow was measured during a FVC maneuver in accordance with the standardized clinical spirometry protocol for measuring FVC established by the American Thoracic Society (ATS; 1995). The following procedures were used to ensure accurate and reliable results: 1) a minimum of three technically acceptable maneuvers were obtained; i.e., the patient maintained an adequate seal around the mouthpiece, was sitting upright and was cued to perform the maneuver with maximal exertion, and expiratory efforts greater than six seconds in duration were recorded; 2) the two highest values agreed within 5% (or ≤ 200 ml with an FVC > 2.0 liters) ; 3) the highest of these two values was quoted and used in the analysis.

- b. Maximum Insufflation Capacity (MIC) is the maximum volume of air stacked within the patient's lungs beyond spontaneous vital capacity. This procedure was based on the work of Bach (1993) and Kang and Bach (2000). MIC was measured in litres using a spirometer and a PCF meter.
- c. Resting Tidal Volume is the amount of air exhaled during a single expiratory cycle at rest over the course of 30 seconds. A minimum of six cycles were recorded.

The Wright Mark 14 Spirometer (Ferrais Development and Engineering Co, Ltd: London, UK) is a mechanical device that relies on the kinetic energy and velocity of the airstream to rotate a light vane housed within a cylinder (Kwong, 2003). According to the manual, the movement of the vane continuously records volumes from 0-10 L in .01 L increments. This instrument responds to airflow in only one direction. The volume of expired air is determined by the position of the pointer on the dial face at the end of each test: a paper record of the test is not provided. Flow rates can only be estimated by averaging a given volume over a specified time. According to the manual, the reported accuracy of Wright Mark 14 spirometer is $\pm 2\%$ at 16.00 LPM on continuous flow (and $\pm 5\%$ at 60.00 LPM). The minimum sensitivity of the device is 2.5 LPM and resistance to gas flow is proportional to the square of flow rate and ≤ 2 cm H₂O at 100 LPM. The accuracy and reproducibility of the Mark 14 spirometer was validated by regular calibration checks using a large spirometry syringe (3L). The output read 3L $\leq 3\%$ or ± 90 ml. The Wright Mark 14 spirometer was used in the three previously published studies on LVR in patients with ALS (Bach, 1993; Kang & Bach, 2000; Tzeng & Bach, 2000) and in the pilot study

(Cleary, et al., 2008), making it a logical choice for measuring pulmonary function in the current study.

(2) Sniff Nasal Pressure test (SnP)- SnP is the maximum pressure generated when a patient produces a short, sharp volitional inspiration while sitting upright with a closed mouth and one nostril occluded. The pressure generated while sniffing is hypothesized to reflect alveolar and intrathoracic pressure and is a direct measure of inspiratory muscle strength (Lechtzin, et al., 2002). SnP was measured using a Portable Respiratory Pressure Meter (Micromedical, Kent, UK) with disposable nose plugs. Pressure was measured in cm/H₂O with a transducer via catheter and a nasal plug inserted into one nostril while the other nostril remained open. Prior to testing, the participants were offered tissues and asked to clear their nasal passages. Each participant engaged in four practice trials, during which time the optimal size and shape of the nasal plug was determined by checking the occluded nostril for leaks. Depending on the size and configuration of the participants' nares, one of eight nasal plugs was selected for testing. The maximum value was recorded over the course of 10 trials for each measurement point (baseline, interim, 30 minutes post). The methods used for SnP testing in this study were based on a normative study of 160 healthy participants (Uldry & Fitting, 1995).

(3) Airway Clearance Measures – Airway clearance refers to the ability to clear the lungs, trachea, throat and mouth using maneuvers such as forced expiration, coughing, throat clearing, and hawking. The maximum expiratory flow of each airway clearance behavior was measured with a Health Scan ASSESS Peak Cough Flow meter (Respironics-Phillips Health Care, Murrysville, PA). It was selected for

use in the current study because it is widely used clinically and has been used in several research studies related to LVR and ALS (Bach, 1993; Kang & Bach, 2000; Tzeng & Bach, 2000). The ASSESS Peak Cough Flow meter device provides a logarithmic measurement of the exhaled air by means of a mechanical vane within a vented polycarbonate chamber that slides an indicator upward in 5 L/min increments with low flow and full flow ranges. According to the manufacturer's specifications, this device meets the ATS standards for peak flow meters and has a reported accuracy of $\pm 10\%$ or 20 L/min, whichever is greater, and test – retest reliability of $\geq 95\%$.

The following PCF measures were obtained:

- a. Maximum peak cough flow during augmented coughing (MIC)
- b. Maximum peak cough flow during a series of simple clearance maneuvers, including hawking, throat clearing, forced expiration, coughing and a swallow-cough-swallow (supraglottic swallow) maneuver.

Standardized data collection forms were used and participants received consistent instructions for each task in the protocol. Also consistent procedures were used to ensure that time intervals remained constant both within and across conditions.

4) Participants' Perspectives on LVR – Information was collected from participants using a short interview about history and use of LVR and a Likert-type scale on which participants rated their perceptions of the LVR treatment (see Appendix B). These measures were developed based on a series of questionnaires, rating scales and

semi-structured qualitative interviews used in the pilot study. The process used to develop the rating scales involved content and format development. The content of the questionnaires was based on information gained in conversations with experts in ALS, including two neurologists, a physiatrist, a statistician, a respiratory therapist and two speech-language pathologists. The content was also based on the results of 12 qualitative interviews with individuals with ALS who were doing in LVR and participated in the pilot study that preceded this thesis (Cleary, et al., 2008). The second step comprised the development of items to match the targeted content. A statistician and epidemiologist assisted with item development and formatting. Some of the items included in the pilot study were deleted from the current thesis version to reduce participant response burden (time to complete the questionnaires). In the treatment session, the questionnaires were administered in the baseline session, prior to treatment. In the control session, questionnaires were administered in the time period before the 15 minute assessment measures.

Results

Analysis

Of interest was the effect of LVR on specific dependent variables (i.e., two tests of pulmonary function, four tests of airway clearance and one test of swallowing). Thus, separate two-way repeated measures ANOVA were conducted for each dependent variable. The within-subjects factors were Condition with two levels (treatment and control) and Time with three levels (baseline/Time 1; 15 minutes post-treatment/Time 2; 30 minutes post-treatment/Time 3). The Condition main effect, Time main effect and Condition x Time interaction effects were tested using the

multivariate criterion of Wilks' Lambda, which does not require the assumption of sphericity (Green, Salkind & Akey, 2000). Follow-up tests for significant ANOVA effects were conducted using paired samples t tests. The Bonferroni adjustment procedure was implemented to control for the increased risk of Type I error across the multiple follow-up t tests; that is, the alpha level was made more rigorous on each of the separate tests. The Bonferroni technique involves dividing the common alpha level (.05) by the number of post-hoc t tests conducted (Huck & Cormier, 1996).

The participants' best scores out of three test trials at each time point were used in the analyses. If a participant could not complete a task during any test trial, the participant's performance on that task was excluded from the analysis. Data were excluded on a case-by-case basis for each dependent variable (see each analysis for specific sample size).

Research Question 1: What is the intensity and duration of the LVR treatment effect on standard tests of pulmonary function?

Forced-vital Capacity (FVC). A repeated measures ANOVA was performed with FVC in L/min as the dependent variable. Because of fatigue, 14 participants could not complete the three required testing trials and were excluded from analysis. The final sample size for use in the analysis of FVC was 15.

The main effect of Condition was significant, $\Lambda = .71$, $F(1, 14) = 5.86$, $p = .030$, as was the interaction effect (Condition x Time), $\Lambda = .54$, $F(2, 13) = 5.58$, $p = .018$ (Table 9). Because the main effect was qualified by an interaction, follow-up analysis was focused on the interaction/combined influence of condition and time on FVC. Paired-samples t tests with a Bonferroni adjusted significance level of $(.05/3 =$

$p \leq .016$) revealed a significant difference in mean FVC between treatment and control conditions at time 3, $t(17) = 2.83$, $p = .012$. No other means were significantly different (See Table 10). Distribution of the data is represented by boxplots in Figure 7. The line in the middle of the boxplot represents the median FVC value, the bottom and the top of the box represent the 25th and 75th percentiles, respectively (interquartile range), and the whiskers represent the smallest and largest values that are not outliers (1.5 – 3.0 box lengths) or extreme scores (3.0+ box lengths from the lower edge of the box) (Green et al., 2000).

Table 9

Two Way Repeated Measures ANOVA Table for FVC (n = 15)

Effect	Value*	F	Hypothesis df	Error df	Sig.	Partial Eta ²
Condition	.700	6.000	1	14	.028	.300
Time	.935	.454	2	13	.645	.065
Condition x Time	.543	5.481	2	13	.019	.457

* Wilks' Lambda

Table 10

Means (SD) for FVC (L) (n = 15)

Condition	Baseline (Time 1)	15 Minutes Post- Treatment (Time 2)	30 Minutes Post-Treatment (Time 3)
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LVR Treatment	2.23 (.93)	2.3 (.92)	2.25 (.95)
Control	2.11 (.86)	2.11 (.83)	2.14 (.82)

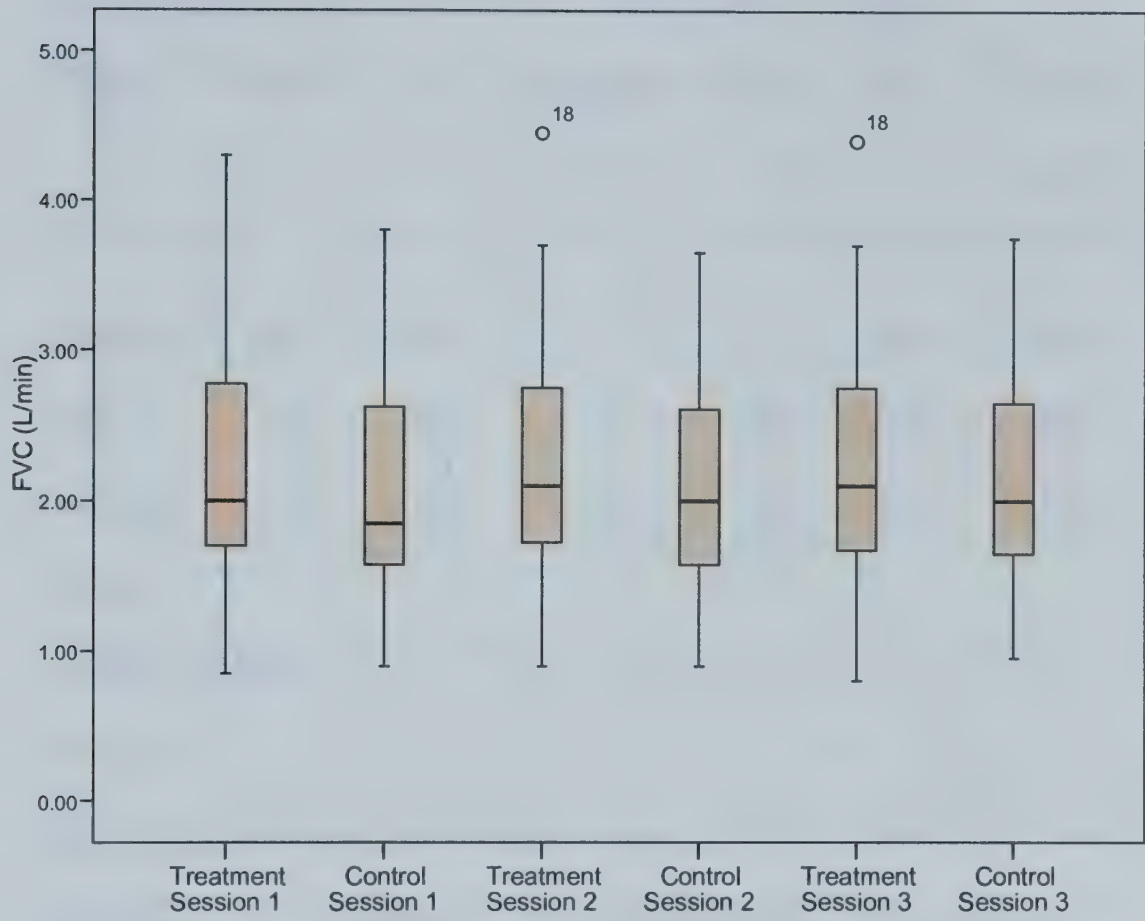


Figure 7. Boxplots of FVC (L/min) by treatment condition (n = 15).

Sniff Nasal Pressure (SnP). After excluding missing data, the sample size for this analysis was 22 (7 individuals could not complete the required number of testing trials). The RM-ANOVA revealed a significant Condition x Time interaction, $\Lambda = .69$, $F(2,21) = 4.92$, $p = .018$. However, when paired t tests were conducted using a significance criterion of .016 (.05/3), none of the means differences between conditions reached significance (Table 11). Table 12 shows the means and standard

deviations by time and condition. Figure 8 represents the boxplot of the data (median and interquartile range) by experimental condition.

Table 11

Two Way Repeated Measures ANOVA Table for SnP (cm/H₂O)

Effect	Value*	F	Hypothesis df	Error df	Sig.	Partial Eta ²
Condition	.941	1.320	1	21	.264	.059
Time	.965	.359	2	20	.703	.035
Condition x Time	.667	4.998	2	20	.017	.333

* Wilks' Lambda

Table 12

Mean (SD) SnP Values (cm/H₂O) (n = 22)

Condition	Baseline (Time 1)	15 Minutes Post- Treatment (Time 2)	30 Minutes Post-Treatment (Time 3)
LVR Treatment	30.81 (21.7)	32.91 (22.3)	32.64 (23)
Control	31.45 (21.8)	30.36 (20.3)	30.86 (19.9)

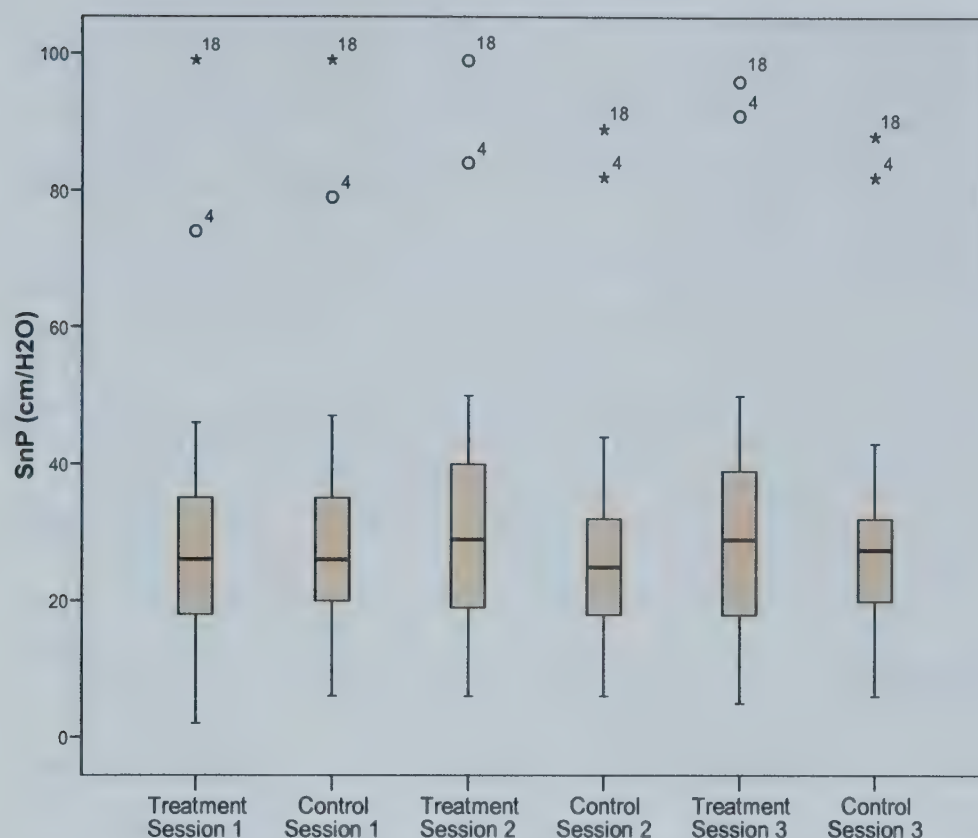


Figure 8. Boxplots of SnP (cm/H₂O) by experimental condition (n = 22).

Correlation between Pulmonary Function Measures. Also of interest was the relationship between FVC and SNP scores as measures of pulmonary function. The mean baseline score in each of the treatment and control sessions was used as the variable in the correlational analysis. The nature of the bivariate relationship between the variables was graphed, revealing a linear relationship suitable for analysis with a parametric correlation technique. The *Pearson Product Moment Correlation* coefficient was computed and revealed a significant positive relationship between the two measures ($r = .81$, $p = .000$) (see Figure 9).

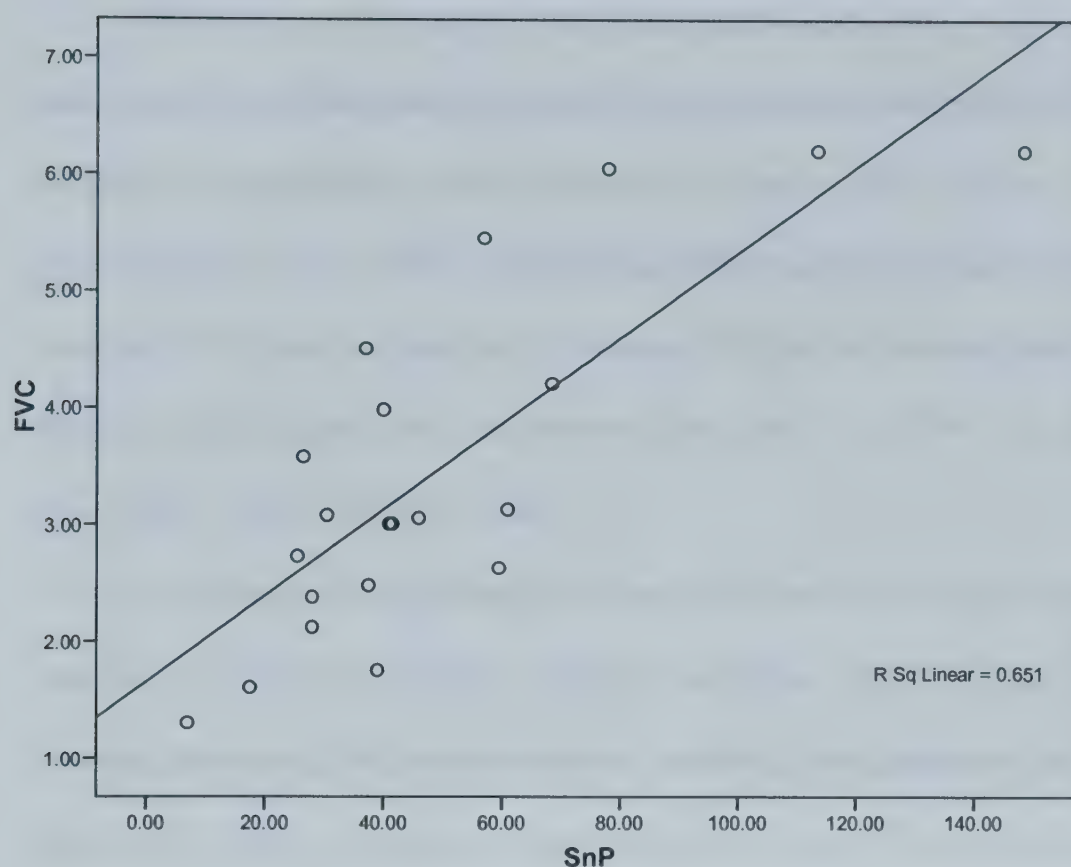


Figure 9. Correlation between FVC (L/min) and SnP (cm/H₂O).

Research Question 2: What is the effect of LVR on unassisted coughing and other volitional airway clearance behaviours (i.e., hawking, throat clearing, forced expiration)?

Coughing. Peak cough flow (PCF) during unassisted coughing was used as the dependent measure. Three individuals were unable to complete the unassisted coughing task; therefore, the sample size for this analysis was 26. The two way repeated measures ANOVA (Table 13) revealed that the Condition main effect was significant, $\Lambda = .64$, $F(1,25) = 14.20$, $p = .001$, the Time main effect was significant, $\Lambda = .42$, $F(2,24) = 16.78$, $p = .000$ and the Condition x Time interaction was significant, $\Lambda = .40$, $F(2,24) = 18.08$, $p = .000$.

Follow-up paired-sample t tests with a significance level of .008 (.05/6) were used. Significant differences were found in mean unassisted coughing flow rates between the treatment and control conditions at time 2, $t(25) = 5.88$, $p = .000$ and time 3 $t(28) = 3.23$, $p = .003$. No significant differences were found between the baseline PCF scores as a function of condition. Within the treatment condition, significant differences were found between time 1 and 2, $t(27) = -6.51$, $p = .000$, and time 1 and 3, $t(28) = -6.23$, $p = .000$.

Participants had significantly higher PCF rates in the treatment condition as compared to the control condition at times 2 and 3 (see Table 14 for means and standard deviations). Within the treatment condition, participants also had significantly higher coughing flow rates immediately and 30 minutes after treatment as compared to baseline. No significant decrease in PCF was noted over the 30 minute interval between time 2 and time 3. See Figure 10 for boxplot distribution (median and interquartile range) of PCF – Unassisted coughing data by experimental condition.

Individual level data were also analyzed (see Figure 11). In the LVR condition, 11 participants (38%) were below the threshold of 180 L/min at baseline. Of these, only five remained below threshold at time 2 (18%), and six were below threshold at time 3 (21%). No individual who produced baseline PCFs >180 L/min had flow rates < 180 L/min at subsequent time points.

In the control condition, eight participants produced PCFs below the threshold of 180 L/min at times 1, 2, and 3. Six of the eight participants who had baseline levels

below 180 L/min continued with below threshold flow rates at time 2, whereas all eight who had baseline rates below 180 L/min produced sub-threshold rates at time 3.

Table 13

Two Way Repeated Measures ANOVA for PCF - Unassisted Coughing

Effect	Value*	F	Hypothesis df	Error df	Sig.	Partial Eta ²
Condition	.941	1.320	1	21	.264	.059
Time	.965	.359	2	20	.703	.035
Condition x Time	.667	4.998	2	20	.017	.333

*Wilks' Lambda

Table 14

Means (SD) for PCF Unassisted Coughing (L/min) (n=26)

Condition	Baseline (Time 1)	15 Minutes Post- Treatment (Time 2)	30 Minutes Post- Treatment (Time 3)
LVR Treatment	251.35 (118.55)	305.00 (140.70)	295.38 (122.99)
Control	263.08 (130.24)	255.19 (120.90)	259.62 (122.25)

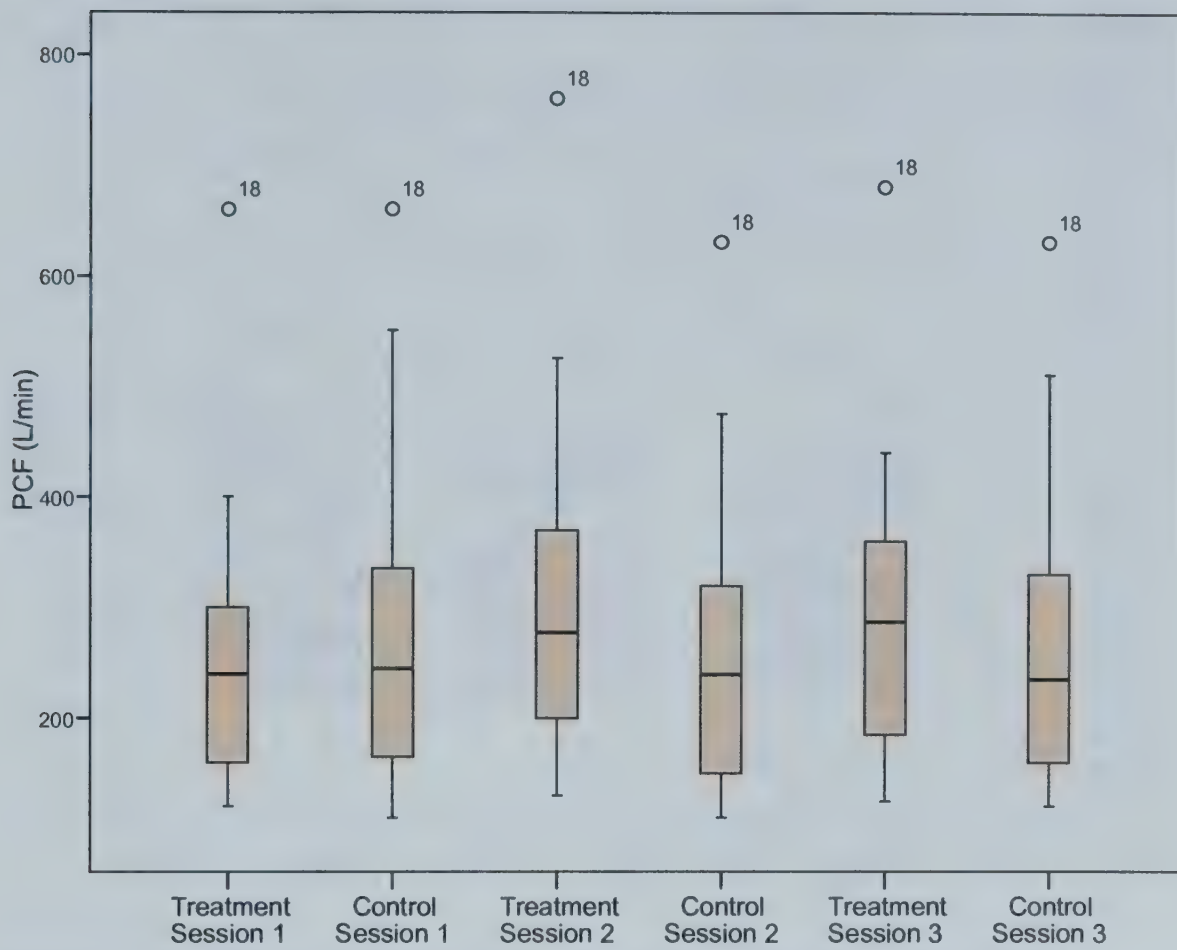


Figure 10. Boxplots of PCF – unassisted coughing by experimental condition (n =26)

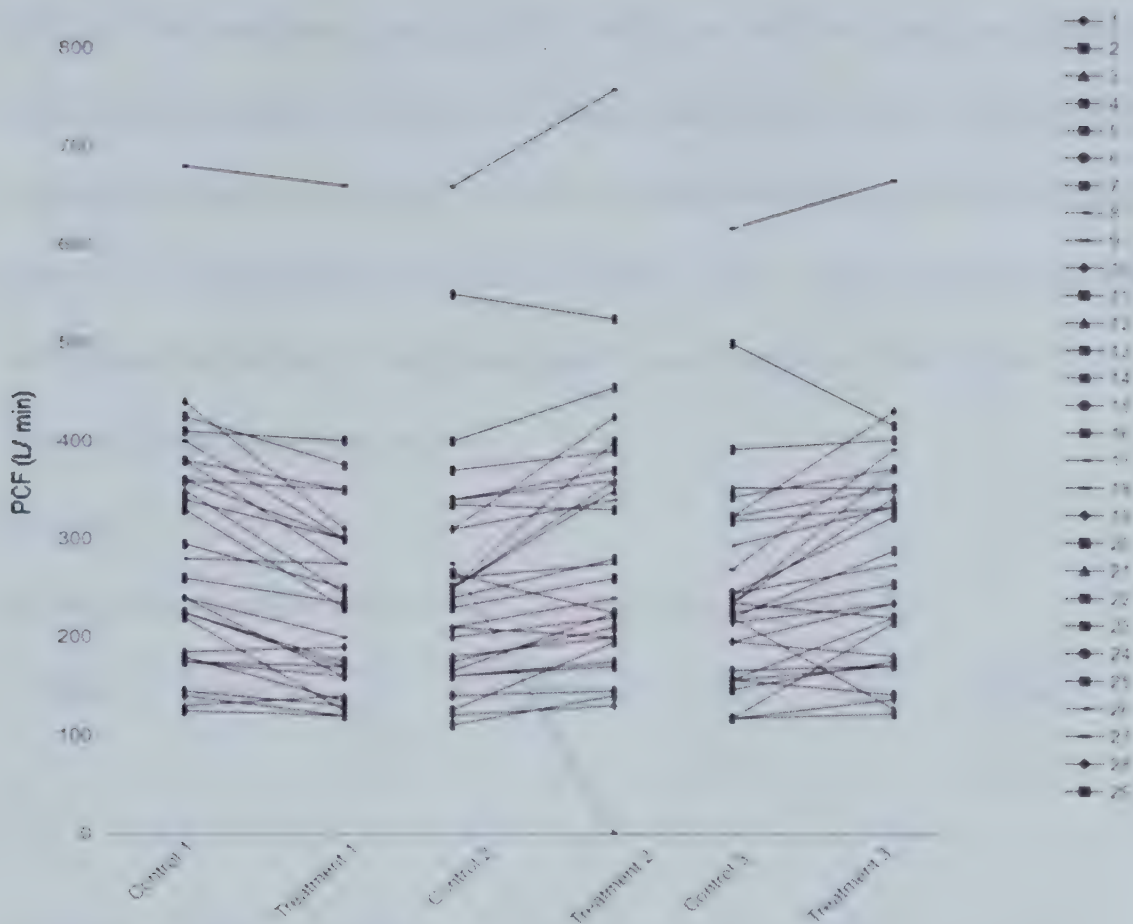


Figure 11. Individual PCF (L/min) – unassisted coughing data ($n = 29$).

Hawking. Twenty-one participants completed the hawking tasks. The RM-ANOVA for hawking (Table 15) revealed a significant main effect of Condition, $\Lambda = .69$, $F(1,20) = 9.03$, $p = .007$, Time, $\Lambda = .68$, $F(2,19) = 4.626$, $p = .023$, and Condition x Time, $\Lambda = .40$, $F(2,19) = 14.26$, $p = .000$. Follow-up analysis was focused on the interaction effect. Paired-sample t tests were conducted with a criterion for significance of .008 (.05/6). Significant differences were found in mean hawking flow rates between the treatment and control conditions at time 2, $t(21) = 4.84$, $p = .000$ and time 3, $t(23) = 4.23$, $p = .000$. No significant differences were found between the baseline flow rates as a function of condition. Within the treatment condition, significant differences were also found between time 1 and 2, $t(22) = -$

4.67, $p = .000$, and time 1 and 3, $t(22) = -4.85$, $p = .000$. No significant difference existed between mean PCF scores 15 (time 2) and 30 minutes after treatment (time 3). In the control condition, hawking flow rates decreased significantly from baseline (time 1) to 30 minutes (time 3), $t(22) = -2.92$, $p = .007$. Table 16 shows that means and standard deviations at each time point in each condition. (See Figure 12 for boxplot distribution of the data).

Table 15

Two way repeated measures ANOVA for PCF Hawking ($n = 21$)

Effect	Value*	F	Hypothesis df	Error df	Sig.	Partial Eta ²
Condition	.689	9.027	1	20	.007	.311
Time	.673	4.626	2	19	.023	.327
Condition x Time	.400	14.257	2	19	.000	.600

Table 16

Means (SD) for PCF Hawking in (L/min) ($n = 21$)

Condition	Baseline (Time 1)	15 Minutes Post- Treatment (Time 2)	30 Minutes Post- Treatment (Time 3)
LVR Treatment	116.19 (58.4)	156.67 (54.5)	148.33 (56.3)
Control	134.29 (64.1)	123.09 (55.8)	120.00 (52.5)

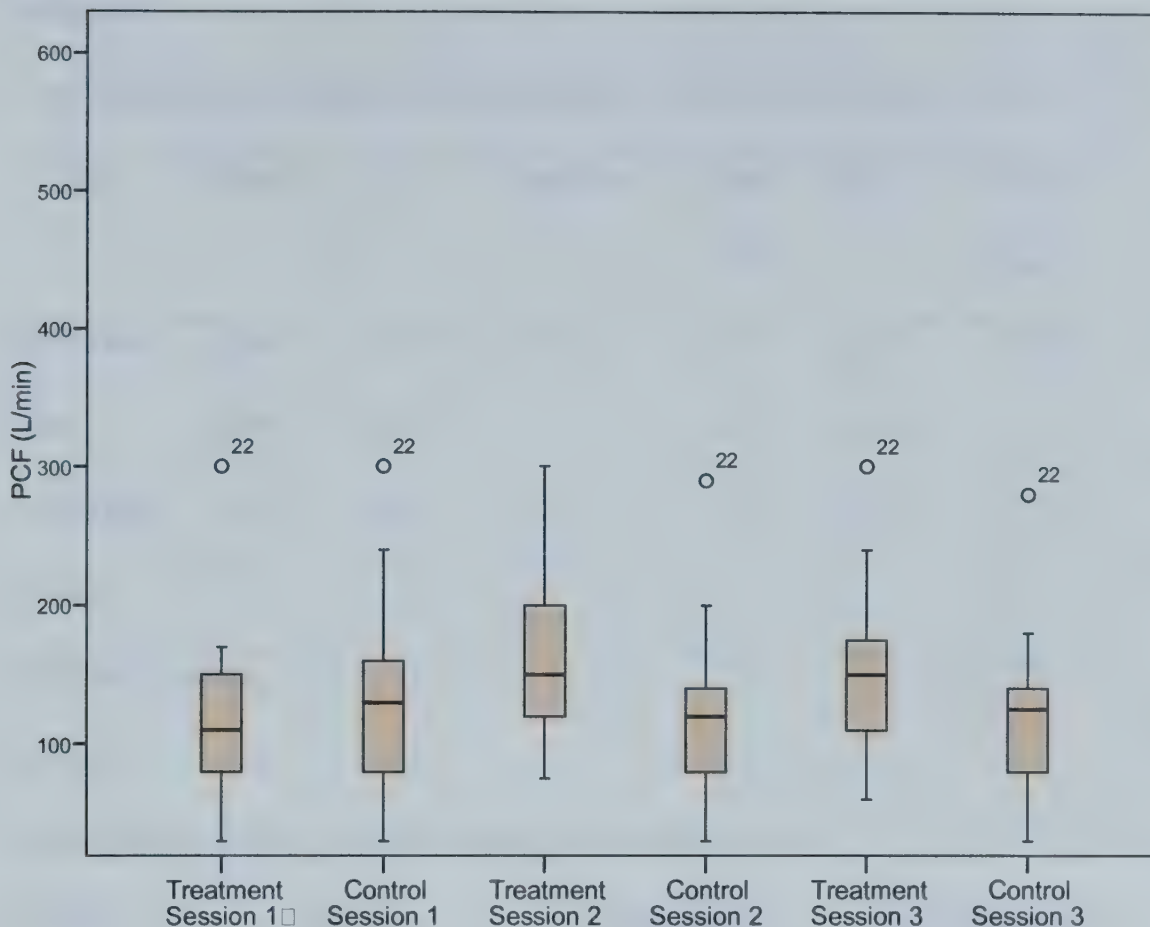


Figure 12. Boxplots of PCF – hawking by experimental condition (n = 21).

Throat Clearing. Twenty four participants completed the throat clearing tasks.

The repeated measures ANOVA revealed a significant main effect of Time, $\Lambda = .59$, $F(1,23) = 7.64$, $p = .003$, and a significant interaction effect (Time x Condition), $\Lambda = .67$, $F(2,22) = 5.49$, $p = .012$ (see Table 17). Follow-up analysis revealed a significant difference in mean throat clearing PCF between the treatment and control conditions at time 2, $t(24) = 3.53$, $p = .002$. Within the treatment condition, significant differences were also found between time 1 and 2, $t(26) = -4.55$, $p = .000$, and time 1 and 3, $t(26) = -4.60$, $p = .000$ (see Table 18 for means and standard deviations for PCF throat clearing) at each time point in each condition. Figure 13 depicts the distribution of the data in boxplots (median, interquartile range).

Table 17

Two Way Repeated Measures ANOVA PCF - Throat Clearing (n = 24)

Effect	Value*	F	Hypothesis df	Error df	Sig.	Partial Eta ²
Condition	.860	3.757	1	23	.065	.140
Time	.590	7.645	2	22	.003	.410
Condition x Time	.667	5.491	2	22	.012	.333

* Wilks' Lambda

Table 18

Means (SD) for PCF Throat Clearing (L/min) (n = 24)

Condition	Baseline (Time 1)	15 Minutes Post- Treatment (Time 2)	30 Minutes Post- Treatment (Time 3)
LVR Treatment	160.42 (65.6)	204.58 (77.8)	190.84 (62.9)
Control	167.71 (72.5)	165.42 (71.0)	172.29 (113.9)

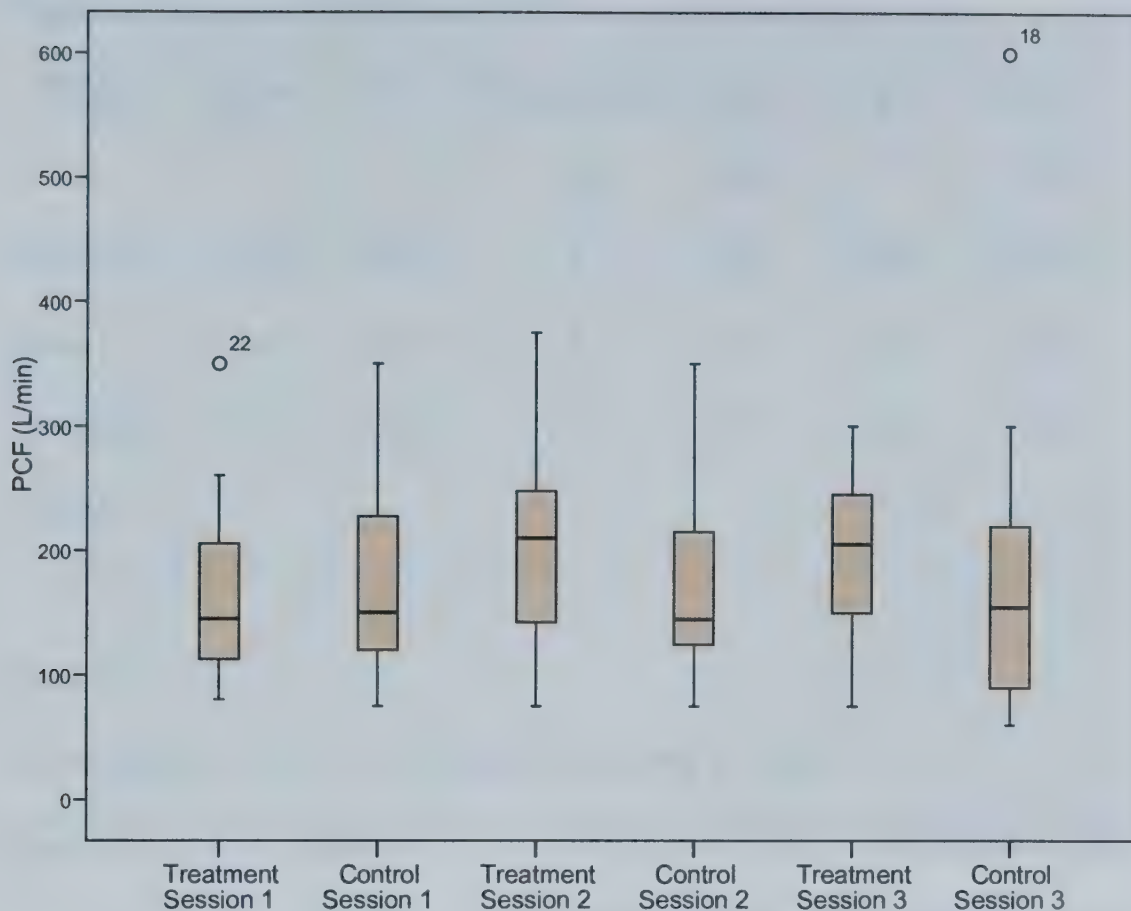


Figure 13. Boxplots of PCF – throat clearing by experimental condition (n = 24).

Forced Expiration. Twenty four participants completed the forced expiration tasks. The repeated measures ANOVA (Table 19) revealed a significant main effect of Condition, $\Lambda = .81$, $\underline{F}(1,23) = 5.53$, $p = .028$, Time, $\Lambda = .74$, $\underline{F}(2,22) = 3.88$, $p = .036$ and Condition x Time, $\Lambda = .56$, $\underline{F}(2,22) = 8.82$, $p = .002$. Follow-up analysis (paired-samples t tests with $p \leq .008$) showed significant differences in mean forced expiration PCF between the treatment and control conditions at time 3, $t(26) = 3.79$, $p = .001$. Within the treatment condition, significant differences were noted between times 1 and 2, $t(27) = -3.38$, $p = .002$, and times 1 and 3, $t(26) = -4.81$, $p = .000$. Table 20 shows the means and standard deviations for forced expiration across time and condition; Figure 14 shows the boxplot distribution of the data.

Repeated Measures ANOVA for PCF Forced Expiration (n = 24)

Effect	Value*	F	Hypothesis	Error	Sig.	Partial
			df	df		Eta ²
Condition	.806	5.531	1	23	.028	.194
Time	.739	3.881	2	22	.036	.261
Condition	.555	8.824	2	22	.002	.445
x Time						

Table 20

Means (SD) for PCF Forced Expiration (L/min) (n = 24)

Condition	Baseline	15 Minutes Post-	30 Minutes Post-
	(Time 1)	Treatment (Time 2)	Treatment (Time 3)
LVR Treatment	217.08 (115.4)	249.38 (110.8)	251.04 (112.1)
Control	223.54 (113.2)	214.79 (115.4)	218.13 (113.8)

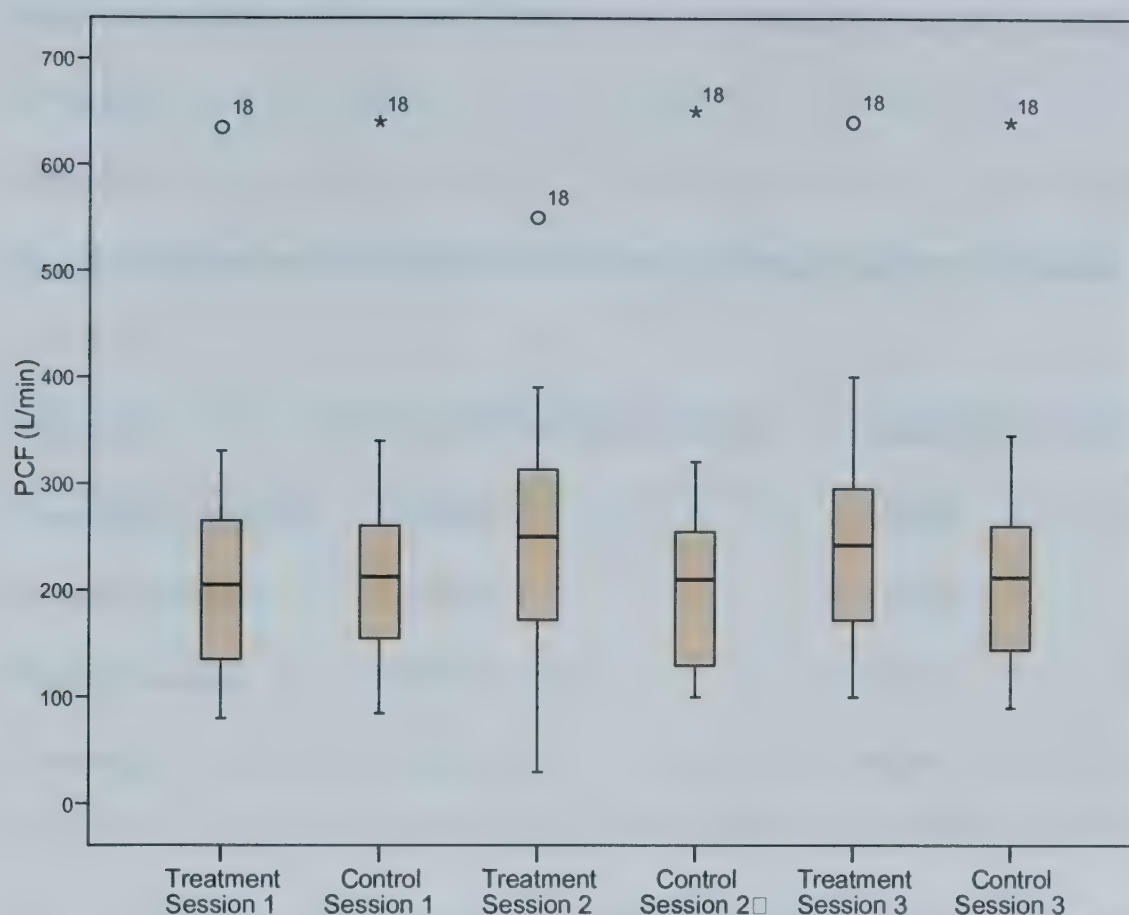


Figure 14. Boxplots of PCF – forced expiration by experimental condition (n = 24).

In summary, LVR had a significant facilitative effect on flow rates during unassisted coughing, as well as other airway clearance maneuvers. Participants experienced an increase in PCF from baseline to post-treatment time points in the LVR condition and these mean flow rates did not decrease significantly over the 30 minute testing interval from time 2 to time 3.

Mean PCF rates varied as a function of each airway clearance maneuver. The baseline values of flow rates for each of the maneuvers were averaged across treatment and control sessions (to create one composite baseline measure for each of the maneuvers). Then, these values were compared. Significant differences were noted between mean PCF for all maneuvers ($p \leq .008$), with the highest mean flow

rates for coughing, followed by forced expiration, throat clearing and hawking (see Table 21).

Table 21
Means and Standard Deviations for PCF Across Airway Clearance Maneuvers
(*n* = 25)

Maneuver	Mean Flow Rates (L/min)	Standard Deviations
Unassisted Coughing	264.00	123.85
Forced Expiration	224.70	111.58
Throat Clearing	167.10	66.02
Hawking	123.50	54.80

Predictors of treatment effect. Potential predictors of successful response to treatment were of interest in the current study. The primary question of interest with relation to predictors of a treatment effect was the following: *How accurately can performance on PCF – Unassisted coughing outcomes be predicted from a linear combination of specific variables?*

To assess the relative contribution of certain variables to a positive outcome of LVR on unassisted coughing, a bivariate correlation analysis was conducted between each potential predictor variable and the criterion/outcome variable. Scatterplots between the predictor and criterion variables were first analyzed for nonlinearity. The initial predictors included were selected based on a theoretical relationship between the predictor and criterion variables: SnP (baseline), FVC (baseline % predicted), ALSFRS Total Score, Age, and Duration of Use of LVR. The criterion variable was

PCF – unassisted coughing value at Time 3 (30 Minutes Post-treatment) in the treatment session. A multiple regression analysis was conducted (with a listwise deletion, yielding a sample size of 27) to evaluate how well these indices predicted positive PCF outcomes. The linear combination of variables was significantly related to PCF – unassisted outcomes at Time 3 ($F_{5,21} = 7.001$, $p = .001$). The sample multiple correlation coefficient was $r = .721$, indicating that approximately 63% of the variance (r^2) in PCF – unassisted coughing at Time 3 can be accounted for by the linear combination of two pulmonary function measures, LVR duration of use, age, and the global severity (ALSFRS) measure.

In Table 22, the relative strength of the individual predictors is presented. The relative weights of the predictors in the regression equation are represented by the standardized Beta coefficients in Table 22. Bivariate and partial correlations are also presented. Two of the five predictors, SnP and PCF, had statistically significantly Beta weights, bivariate and partial correlations with PCF – unassisted coughing (Time 3). SnP alone accounted for 53% of the variance in PCF outcome. Based on these results, it appears that the two pulmonary function measures are the most useful predictors of PCF – unassisted coughing outcomes. However, it is difficult to make judgments about the relative contributions of SnP and FVC because they are correlated ($r = .45$; $p = .01$) (Salkind, et al., 2000). No other correlations were statistically significant among the predictor variables.

In summary, results of the multiple regression analysis suggest that if an individual has better pulmonary function, s/he will have a better response to LVR treatment, as measured by higher PCF values during unassisted coughing at 30

minutes after LVR training, which translates to more effective airway clearance abilities compared to individuals with lower pulmonary function scores.

Table 22

Beta Weights, Bivariate and Partial Correlations of the Predictors with the PCF – Unassisted Coughing Outcome at Time 3 (n = 27)

Predictors	Beta coefficient (standardized weights)	Correlation between each predictor and the PCF time 3 values (bivariate)	Correlation between each predictor and PCF Time 3 values controlling for all other predictors (partial)
Age	-.034	-.100	-.030
ALSFRS – Total score	.064	.065	.064
LVR	.093	-.040	.140
Duration of use (days)			
FVC (% predicted at baseline)	.339**	.581**	.292*
SnP (baseline)	.584**	.727**	.492**

* $p < .05$, ** $p < .001$

A discriminant analysis was also conducted to determine whether the five predictors could predict improvement in PCF from baseline to time 3, in terms of percentage of the original baseline score. The purpose of this analysis was to

determine if the use of these predictors would help differentiate the participants into two groups: those who showed an improvement at Time 3 PCF during unassisted coughing of >15% over baseline and those whose improvement was <15% over baseline.

Twenty-seven participants were able to be classified into one of these two groups. When the discriminant analysis was performed, the overall Wilks' Lambda was not significant, $\Lambda = .64$, $X^2(5, N = 27) = 10.05$, $p = .074$ indicating that the overall predictors did not differentiate among the two groups.

When we attempted to predict group membership using the predictor function, we were able to correctly classify 81.5% of the sample (Table 23) using the five predictor variables originally used in the regression analysis. To correct for chance agreement, a kappa coefficient was computed. Kappa ranges in value from -1 to +1, with 1 indicating perfect prediction, 0 indicating chance level prediction and negative values indicating poorer than chance prediction (Salkind et al., 2000). Kappa was .42, a moderate value.

Table 23

Group classification for discriminant analysis (n = 27)

		Predicted Group Membership		Total
		< 15%	> 15%	
Count	less than 15%	10	3	13
	greater than 15%	2	12	14
%	less than 15%	76.9	23.4	100
	greater than 15%	14.3	85.7	100

Maximum Insufflation Capacity (MIC). MIC was also tested when participants engaged in LVR treatment. Although none of the participants was able to complete the three test trials necessary to meet ATS Criteria (1994), an exploratory analysis was conducted to examine if there was a mean difference between MIC scores and mean baseline FVC scores in the LVR treatment condition. Mean volumes were compared using a paired samples t test. The means were significantly greater when participants were manually insufflated, $t(18) = -5.31, p = .000$.

Research Question 3: What is the effect of LVR on a specific compensatory swallowing technique (i.e., supraglottic swallow maneuver)?

Nineteen participants completed the supraglottic swallow maneuver and their results were included in the analysis. The repeated measures ANOVA (Table 24) revealed a significant main effect of Condition, $\Lambda = .61, F(1,18) = 11.49, p = .003$, Time, $\Lambda = .40, F(2,17) = 12.60, p = .000$ and Condition $\times$ Time, $\Lambda = .45, F(2,17) = 10.42, p = .001$. Follow-up analysis was focused on the interaction effect. Paired-samples t tests were conducted ($.05/6 = .008$). Significant differences were found in mean PCF during the supraglottic swallow between the treatment and control conditions at time 2, $t(21) = 4.24, p = .000$ and time 3, $t(23) = 4.41, p = .000$. No significant differences were found between the baseline flow rates as a function of condition.

Within the treatment condition, significant differences were found between time 1 and 2, $t(22) = -5.78, p = .000$, and time 1 and 3, $t(25) = -4.98, p = .000$. No

significant decrement was noted in mean supraglottic swallow flow rates over 30 minutes (from time 2 to time 3). Table 25 shows the means and standard deviations for supraglottic swallowing across time and condition. Figure 15 is the data distribution in boxplots (median, interquartile range).

Table 24

Repeated Measures ANOVA for PCF Supraglottic Swallow Maneuver (n = 19)

Effect	Value*	F	Hypothesis df	Error df	Sig.	Partial Eta ²
Condition	.610	11.488	1	18	.003	.390
Time	.403	12.599	2	17	.000	.597
Condition x Time	.449	10.417	2	17	.001	.551

*Wilks' Lambda

Table 25

Means (SD) for PCF - Supraglottic Swallow Maneuver (L/min) (n=19)

Condition	Baseline (Time 1)	15 Minutes Post - Treatment (Time 2)	30 Minutes Post - Treatment (Time 3)
LVR Treatment	265.00 (147.4)	310.26 (151.9)	304.47 (139.5)
Control	267.64 (134.0)	261.58 (134.3)	269.47 (138.9)

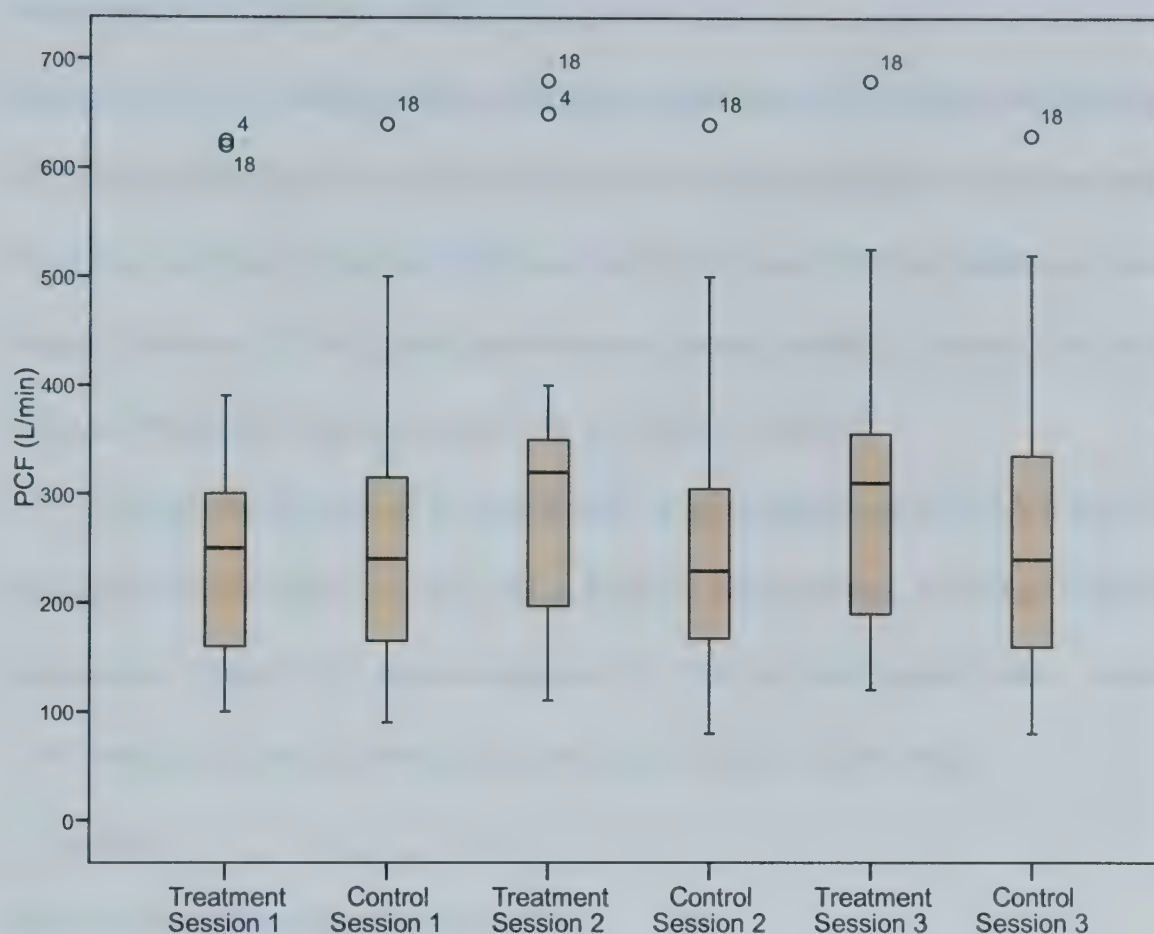


Figure 15. Boxplots PCF – supraglottic swallow maneuver by experimental condition (n = 19).

Research Question 4: What are participants' perspectives on the effects of LVR on their breathing, swallowing and secretion management?

To answer this question, participant responses to the interview on history and use of LVR and the rating scale regarding therapeutic effects of LVR will be summarized descriptively. Except where indicated, all participants completed the questionnaires and interviews (n = 29).

History and Use of LVR. At the start of the study the participants had been performing LVR for 4.8 months on average ($SD = 7.0$) and length of use ranged from 10 days to 32 months. Thirty-four percent of the participants had been doing LVR ≤ 1

month and 17 % had been doing LVR for more than six months. When asked how frequently they performed LVR, most participants reported doing three sessions per day and three trials per session. LVR was routinely done prior to mealtimes and the most frequent time of the day LVR was performed was in the late afternoon prior to dinner. However, 50% of participants reported some variability in both the time of day and frequency of use from week to week (See Table 26).

Sixty nine percent of the participants were independent with LVR and 31% required the assistance of a caregiver to perform the treatment. Most participants used the standard ‘duck-bill’ type mouthpiece (79.3%), two participants used a ‘scuba-type’ mouthpiece and the remaining four subjects used a face mask.

Table 26

Self-reported History and Use of LVR

Average # sessions/day	Frequency	Percentage Reporting (%)
	3	51.9
	2	37
	4	7.4
	1	3.7
Average # trials/session		
	3	39.1
	4	34.8
	5	21.7
	1	4.3
Typical time each day		

PM/before dinner	28.8
Upon waking	25.8
AM/before lunch	22.7
Before bedtime	10.6
Eve/after dinner	7.6
Mid-afternoon	4.5
Consistency of use: same time each day	
Very consistent	28.7
Somewhat	54.6
Not consistent	16.7
Consistency of use: same # of sessions per week	
Somewhat	50.0
Very consistent	28.6
Not consistent	21.4

When asked to characterize the amount, consistency and source of secretions cleared from the airway during LVR, over 70% reported no mucous expectoration from either the lungs or the throat during a typical treatment session. Eighteen percent of participants reported clearing “a little” of mostly thick mucous from the lungs and 22% reported clearing “a little” of mostly thin secretions from the throat. See Table 27 for specific results related to secretion clearance during a typical LVR session.

Table 27

Self-reported Secretion Clearance during LVR

	Frequency	Percentage Reporting (%)
Amount of mucous cleared from <u>lungs</u> during a typical session		
	None	71.4
	A little	18.0
	It varies	7.0
	A lot	3.6
Amount of mucous cleared from <u>throat</u> during a typical session		
	None	70.4
	A little	22.2
	It varies	7.4
	A lot	0
Consistency of secretions cleared from <u>lungs</u> during a treatment		
	Thick	50
	Combination	37.5
	Thin	12.5

Consistency of secretions cleared from
throat during a treatment

Thick	12.5
Combination	37.5
Thin	50.0

Participants were asked to describe how they felt after a typical treatment session. The majority (19/29 or 66%) of participants reported positive feelings. Eleven participants (35%) reported feeling refreshed, six (24%) described the sensation of a cleared airway and two (7%) made other positive comments such as “I feel a lack of restraint, my breathing is deeper, and I get more air into my lungs” (Participant 22) and “I can feel that it is stretching my lungs, it really helps” (Participant 28). However, 10 participants, or approximately 1/3 of the sample reported negative perceptions of the treatment effects. Four reported being tired after LVR, and the other six made various comments such as the following: “I get air in my stomach” (Participant 11), “The cleared airway only lasts for about one minute, then it’s all back again” (Participant 1), and “I feel phlegmy” (Participant 6).

Therapeutic effects of LVR. The majority of respondents (62.1 % =18) agreed that LVR helped them to keep their airway clear. However, only 30% of participants agreed that LVR helped to clear both thick and thin secretions from their throats, and approximately 25% of the group thought LVR helped them clear thick mucus from their lungs.

Regarding the effect of LVR on feelings of anxiety and fear, the results were mixed. Fifty percent of the sample agreed that they have less fear of being very short

of breath because of LVR therapy, yet 32.1 % were neutral/uncertain and 17.9% disagreed that LVR had an impact on their fear of being short of breath. A large percentage of respondents (71.8%) disagreed that LVR therapy makes them more anxious about their breathing, but only 35.4% agreed that it makes them less anxious about managing excess secretions. Likewise, only 21.4% agreed that LVR decreased their feelings of fear about choking.

With regard to the effect of LVR on phonatory function, approximately half of the sample was neutral/uncertain or disagreed with the statements that LVR improved vocal loudness and quality. Forty-three to 44% agreed or strongly agreed that it improved these aspects of their voice.

Table 28

Participant Perspectives on the Therapeutic Effects of LVR

Questionnaire Item	Strongly Disagree	Disagree	Neutral/ Uncertain	Agree	Strongly Agree
LVR therapy helps					
me to keep my	0.0	0.0	37.9	48.3	13.8
airway clear					
LVR helps me clear					
thin secretions from	3.4	6.9	55.2	34.5	0.0
my throat					
LVR helps me clear					
thick mucous from	6.9	6.9	55.2	27.6	3.4
my throat					

LVR helps me clear					
thick mucous from	3.4	10.3	62.1	17.2	6.9
my lungs					
LVR <u>does not</u>					
improve the strength	13.8	37.9	24.1	20.7	3.4
of my cough					
LVR improves the					
loudness of my	0.0	7.1	46.4	39.3	7.1
voice*					
LVR improves the					
quality of my voice	0.0	6.9	48.3	41.4	3.4
LVR therapy makes					
me <u>more</u> anxious	25.0	46.8	14.3	10.3	3.4
about my breathing*					
LVR therapy makes					
me less anxious about					
managing excess	3.4	10.3	51.7	31.0	3.4
secretions					
I have less fear of					
choking because of	3.6	21.4	53.6	21.4	0.0
LVR therapy*					

I have less fear of					
being very short of	3.6	14.3	32.1	35.7	14.3
breath because of					
LVR therapy*					

*n = 28

Participants were also asked to rate changes in cough strength and voice quality after LVR. As a group, the participants most frequently characterized strength of cough as “fair” before performing LVR therapy and “good” immediately after LVR therapy. Nineteen participants indicated a positive change in cough strength after LVR, with two participants indicating a two category improvement and another indicating a three category improvement; nine participants indicated no change in cough strength after LVR. Twenty one participants indicated no change in voice quality after LVR; 7 participants indicated a positive change in voice quality after LVR, with three participants indicating a two category improvement (see Table 29).

Table 29

Self-rated change in Cough Strength and Voice Quality after LVR

Questionnaire Item	Excellent	Very Good	Good	Fair	Poor
Please estimate the					
average strength of your					
cough <u>before</u> you do	0.0	0.0	28.6	50.0	21.4
LVR					

Please estimate the					
average strength of your					
cough <u>immediately after</u>	3.6	10.7	64.3	14.3	7.1
you do LVR					
Please estimate the					
quality of your voice	3.6	0.0	42.9	39.3	14.3
<u>before</u> you do LVR					
Please estimate the					
quality of your voice					
<u>immediately after</u> you do	3.6	7.1	53.6	32.1	3.6
LVR					

Discussion

The primary aim of this study was to evaluate the effects of LVR on respiratory and swallowing function in individuals with ALS. The main findings were as follows: 1) LVR had a significant positive effect on FVC immediately after treatment only and did not have a facilitative effect on SnP at any time point; 2) LVR had an significantly positive effect on unassisted coughing, hawking, throat clearing, and forced expiration, at time 2 (immediately after treatment) and time 3 (30 minutes post treatment); 3) LVR had an significantly positive effect on PCF measured during the supraglottic swallow maneuver, immediately after and 30 minutes post-treatment; 4) Participant perceptions of LVR were mixed. The majority of participants expressed satisfaction with LVR, indicating that they tolerated the treatment well, and that they

perceived positive effects on cough strength and the ability to clear the airway. However, the large majority of the sample reported that LVR was not helpful in clearing secretions from the throat and lungs. A minority of participants agreed that LVR lessened their fear and anxiety about choking. These findings have clinical and theoretical implications that will be discussed in the sections that follow.

Findings in the Context of Previous Research

The facilitative effect of LVR on unassisted coughing is consistent with findings from previous research (Bach, 2007; Kang et al., 2005). Researchers who implemented mechanical breath stacking and cough augmentation strategies using positive pressure ventilation (Troussant, 2009; Trebbia, 2005; Bach, 1993) or a combination of mechanical and manual techniques (Bach et al., 1993; Ishikawa, et al., 2008, Kang et al., 2000), also noted increased PCF during cough after the use of breath stacking.

The current study also extends the research in this area in two important ways. First, in addition to coughing, PCF was measured during other airway clearance measures and during a compensatory swallowing strategy. Secondly, the LVR treatment effect was examined immediately and 30 minutes after treatment. In previous studies, researchers collected outcome data at only one time point, immediately following breath stacking or cough augmentation and during coughing only.

The interpretation of PCF data has traditionally been guided by the use of flow thresholds. The mostly widely used PCF clinical guidelines include the following parameters: 160 L/min is considered the minimum flow necessary to clear

the airway (Bach and Saitio) ≥ 80 L/min is considered an effective range for coughing (Toussaint et al., 2009); ≥ 280 L/min is associated with reduced risk of secretion encumbrance and pulmonary infections. In the current study, the group mean crossed the 280 L/min threshold during the LVR treatment condition at time 2 ($\bar{M} = 298$ L/min) and remained elevated at 30 minutes post treatment ($\bar{M} = 290$ L/min). Thus, the range is sufficient to deal with secretion encumbrance and is one that is generally associated with more favorable clinical outcomes.

The lasting treatment effect is important clinically. In general, clinicians and patients are interested in facilitating function for as long as possible after a treatment. If PCF during coughing and other airway clearance behaviours can remain elevated for up to 30 minutes, individuals with ALS may be better able to protect their airway for at least that amount of time, providing improved safety during ADLs, such as eating, and increased efficiency of secretion management during conversations, visits with family, and so on.

As a secondary analysis, several variables were entered into a regression equation. The linear combination of these variables predicted PCF – unassisted coughing at 30 minutes post-treatment in the intervention session. The two factors that explained most of the variance in PCF outcome, and had the strongest relative weights, were baseline measures of SnP and FVC. These factors were theorized to have predictive value, based on the fact that they are measures of respiratory function, which is directly related to the LVR treatment. Severity of ALS was hypothesized to be a predictor of successful response to treatment but was not significantly related. Although FVC values are also considered markers of severity of decline, they differ

from ALSFRS scores which reflect functioning across multiple domains of function. Thus, unsurprisingly, the more closely correlated the variables are to the mechanism of the treatment effect, the stronger the predictive value.

Differential Effects of LVR: Implications for Mechanisms of the Treatment Effect

The size and duration of the LVR treatment effect on PCF may also be important from a theoretical perspective. Although the exact nature of the treatment effect remains unclear, the results of this study support the hypothesis that LVR causes temporary changes in lung and chest wall compliance and elastance (i.e., the forces that oppose stretching). These concepts are discussed in term of the relevance to the outcomes observed in this study.

Compliance refers to distensibility of the lung and chest wall and the ease with which it can stretch to accommodate greater volumes of air. Compliance is specifically defined as the change in lung volume divided by the change in transpulmonary pressure or $\Delta V/\Delta P$ (Lumb, 2000). Compliance is often expressed in units of L/cmH₂O, with a normal value for lung and chest wall compliance at rest being 0.1 L/cmH₂O (Des Jardins, 2002). Compliance measures are derived from analyzing the slope between two points on a pressure-volume curve (i.e., periods of no flow at end-inspiration and end-expiration; Levitsky, 2007). The lungs and chest wall tend to be less compliant at low volumes (due to the difficulty overcoming the initial opposition to expansion) and less compliant at high lung volumes (as the system approaches its maximal range).

Elastance is inversely related to compliance and is a term used to describe the elastic properties of alveoli, lung and chest wall. Lungs with higher compliance tend

to have low elastance. Elastance, then, is specifically defined as the reciprocal relationship of compliance (i.e. $\Delta P/\Delta V$; Lumb, 2000). Elastance has two basic elements: the tendency for the lung and chest wall to oppose stretching (including alveolar surface tension forces that also resists expansion) and the capacity of elastic tissues and materials to return to their original size and resting configuration after the distending force is removed (Lumb). The mechanism by which elastic tissue returns to its original state is explained by the principle of hysteresis. The principles of hysteresis states that elastic tissues demonstrate a ‘memory’ of their recent history and respond differently when contracting after the respiratory system has been perturbed by either a prolonged period of low lung volumes or relatively short periods of high lung volumes, as in the case of LVR (Lumb, 2000). Compliance, elastance and hysteresis, then, are important concepts in explaining the underlying mechanisms of the LVR treatment effect observed in this study. Specifically, the lungs and chest wall were distended by the maximal insufflations of LVR. These short-term changes in compliance lasted for up to 30 minutes and facilitated stronger cough during a variety of airway clearance tasks.

Decreased lung compliance is a hallmark feature of patients with ALS. This reduced compliance is a result of stiffness in the lung and chest wall, atelectasis, and high surface tension of hypoventilated alveoli (Lechtzin et al., 2006). In studies over the last few decades, researchers have demonstrated that reduced compliance may respond to respiratory interventions similar to LVR.

Specifically, in patients with poor lung compliance as a result of restricted lung and chest wall movement and/or recent history of hypoventilation, lung compliance was

temporarily a series of deep sustained inhalations followed by breath-holding (Watson, 1962, Lumb, 2000). In a recent study, Lechtzin et al. (2006) used invasive transdiaphragmatic (Pdi) techniques and spirometry to measure compliance in 14 patients with ALS after they performed a single, 5-minute “supra-maximal inflation” session of non-invasive ventilation (i.e., inspiratory pressures of 22.8 cm/H₂O). An immediate treatment effect was evident, with participants showing an improvement in dynamic lung compliance (treatment effect .29 or 11.3 cm/H₂O). LVR is thought to work through a similar hyper-inflation mechanism that perturbs the system and results in immediate changes in respiratory function.

Although compliance was not optimally assessed in the current study using Pdi, a clinical surrogate measure of compliance was obtained through maximum insufflation capacity (MIC) during the treatment portion of the protocol. Participants demonstrated an immediate change in compliance as demonstrated by increased MIC during the LVR treatment. MIC is considered one of the most widely used ways of determining of the effectiveness of breath stacking techniques. To determine effectiveness, researchers compare the differences between the pre-treatment performance with the “assisted cough” or MIC. MIC is measured when the patient is maximally insufflated via air stacking. The MIC data provide a measure of the extent of the insufflation (i.e., if MIC-FVC = FVC, then the treatment is ineffective).

The MIC maneuver is complicated. It requires that patients have adequate bulbar function to retain the trapped air while simultaneously changing the mouthpiece from the LVR bagger to either the spirometer or the PCF meter. Because of the challenges in conducting MIC testing, missing data are common (Kang &

Bach, 2000; Kang et al., 2005). In the current study only 84% of the participants could perform FVC-MIC and just 58% could complete PCF-MIC. Because of issues related to timing in the protocol, none of the participants had the opportunity to do the three trials required to meet ATS (1996) standards; therefore, these results should be interpreted with caution. The PCF-MIC and the FVC-MIC results of this study appear to fall within the low end of the range of MIC gain scores reported in the literature. Compared to data in the related literature (Kang & Bach 2000; Kang et al.2005), participants in the current study have the highest average baseline levels for both PCF & FVC, perhaps contributing to a ceiling effect in which they had reduced capacity for breath stacking.

Another possible explanation is that in the related studies, investigators used mechanical volume ventilators. These may provide a more consistently timed and calibrated delivery of air, making the procedure more predictable in terms of routine and set-up. The manual bagger used in the current study is effort dependent, self-timed, and patients often need help from others to perform the treatment. The portable nature of the bagger makes it convenient, but also more variable in terms of set-up and positioning.

Participants' familiarity and exposure to other breathing treatments may also explain the differences in MIC levels. Most of the available research was conducted on patients with Duchene Muscular Dystrophy (DM) and related neuromuscular disorders in which patients typically have a long history of noninvasive ventilation. For example, Bach (1993) used manual breath stacking with 13 participants with mixed neuromuscular etiologies who were also long-term NIV users (average age 45

years and a 15 year history of using NIV approximately 21 hours per day). All participants in the Bach et al. (2007) study were ventilator dependent and used glossopharyngeal breathing to decrease daytime ventilator use. In the current study, participants were asked to perform a typical LVR session (i.e., five maximal insufflations with only two PCF-MIC trials and two FVC-MIC trials) and the expectation was that patients were performing LVR approximately three times each day.

Another compelling indicator to support the hypothesis that compliance changed as a result of LVR is the finding of volume changes observed in FVC after the LVR treatment. These volume changes may have contributed to positive cough and airway clearance outcomes of this study. It is probable that mechanical changes related to stress-relaxation played a role in the favorable FVC results.

Stress-relaxation is a function of lung distensibility following inhalation to total lung capacity (Cotes, 1993). The lung and thoracic tissues are initially resistant to stretching, but once the elastin and collagen fibers within the alveoli and surrounding the airways have become distorted, frictional resistance is created. Recoil forces during expiration are reduced as these visco-elastic tissues become reluctant to assume their original size and shape (Lumb, 2000). A similar form of hysteresis occurs at high lung volumes as the surface tension of the surfactant that lines alveoli opposes compression of the alveoli at the beginning of expiration and causes some alveoli to re-distribute air to adjacent alveoli (Des Jardins, 2002). These changes explain in part why the shape of the upper part of the expiratory pressure-volume curve shifts upward and tends to be flatter after deep sustained inspirations and the

width between the two curves becomes wider as compliance improves with enhanced lung volumes. A similar pattern of hysteresis in the pressure-volume curve likely occurred in this study due to the high distending pressures and sustained breath-holding involved in LVR. As lung volumes increase, the alveoli, lung parenchyma, and conducting airway become more patent and easier to inflate. In this study, it is plausible that as the lungs and chest wall became more compliant after LVR, they were easier to fill. Thus, the same amount of distending pressure yielded higher lung volumes and less volume-dependant airway closure.

The pressure – volume curve also demonstrates the principle that compliance varies according to lung volumes and the best compliance is in the middle of the range. Specifically, the steepest part of both slopes tends to fall within 5 to 10 cm/H₂O of transpulmonary pressure (West, 2000). In cases of hypoventilation, any increase in lung volume is likely to place affected patients within a more favorable range on the compliance curve. Compliance is especially poor in patients with low lung volumes at the beginning of inspiration due to resistance to lung expansion caused by the high surface tension of small alveoli and the impedance caused by closed and hypoventilated lung units.

The lung volume at which the alveoli collapse is referred to as closing capacity. Closing capacity increases with age and at the age of 66 (the mean age of participants in this study) healthy individuals experience alveolar closure and airway collapse in dependant parts of the lung during normal tidal breathing at the end of expiration (i.e., functional residual capacity) (Lumb, 2000). Collapsed airways occur at higher lung volumes in patients with chronic hypoventilation. In patients with

Adult Respiratory Distress Syndrome, LVR techniques have been shown to improve lung volume by increasing both number and size of recruited alveoli (Lapinsky & Methe, 2003).

Another mechanism by which volume changes that occur as a result of LVR may improve lung compliance is through elimination of retained secretions and chronic subclinical microatelectasis that have mass additive effects (Lechtzin et al., 2006, Swake et al. 2003). The combined effect of cough augmentation and secretion mobilization that occurs with LVR is particularly effective in clearing accumulated materials such as thick mucus plugs, pus, and other secretion from the pulmonary airways (Guion, 2009). As the airway become more patent airflow velocities increase and airway resistance decreases.

Although we did not directly measure changes in secretion clearance or atelectasis in this study, the majority of participants agreed that LVR helped them to keep their airway clear and PCF were significantly improved. Based on widely accepted principles of respiratory resistance, it is probable that LVR treatment effect was also due in part to a transient decrease in airway resistance in conjunction with enhanced compliance.

Airway resistance (R_{aw}) is defined as the pressure gradient between the alveoli and the mouth divided by rate of airflow (i.e. $(\Delta P_{cmH_2O}/\Delta VL/sec)$ and a normal value in adults is 0.5 to 1.5 cmH₂O/L/sec (Cotes, 1993). As lung volumes decrease, airway resistance increases substantially and the maximal rate of airflow drops rapidly (West, 2000). In this study, LVR was shown to temporarily enhance lung volumes and it this likely contributed to decreased R_{aw} and higher peak expiratory

flow rates. The following section will focus on the PCF results and review four potential mechanisms by which R_{aw} improved as the result of LVR. These include favorable changes in volume – related airway collapse, flow- related airway collapse, compliance of the small airways, contractions of expiratory muscles.

Volume-Related Airway Collapse. Increased R_{aw} due to volume – related airway collapse occurs with low lung volumes because the airways are not held open by mechanical traction of expanded lungs. Any increase in the diameter of the airway as the result of treatments such as LVR would have a profound effect on the velocity of airflow. According to Poiseulles' Law, flow is directly proportional to the pressure change multiplied by the radius of the tube to the fourth power, therefore, if the airways were distended by only 16% over their original size, the rate of airflow would double (Des Jardins, 2002). Although many complex processes influence the diameter of inner lumen of the airways (e.g., bronchial smooth muscle tone, other co-occurring respiratory disorders such as asthma or bronchitis, physical and chemical effect of foreign materials within the airway) lung volume is one the most important factors in determining the presence and degree of volume - related airway collapse (Lumb, 2000).

Flow-Related Airway Collapse. There are two main causes of flow-related airway collapse during expiration. First, due to the Bernoulli Effect, the pressure within the airway drops as a result of frictional resistance and a drop in potential energy created when the column of air accelerates as it moves down the conducting airway (Cotes, 1993). When pressure inside the airway drops below the pressure outside the airway, a choke point is formed. This occurs at a point where the cross-

sectional area of the entire airway dramatically decreases as air moves through multiple generations of small parallel vessels to a few medium and large bronchi, which collectively, have a relatively small cross-sectional area. In healthy adults, flow-related airway collapse occurs in the larger bronchi during forced expiration and coughing and can be observed in flow-volume loops after 30% of vital capacity is expired. This part of a forced expiratory curve is called the effort independent portion because any increase in respiratory muscle effort will not yield any improvement in the rate of flow once a flow limitation is created. In coughing and forced expiration, the maximal flow rates are also volume dependant and determined in large part by the extent of inspiration prior to peak expiratory flow (Lumb, 2000). The highest peak expiratory flow rates observed in flow-volume loops have shortest rise time on the effort-dependant portion of the expiratory curve and are associated with glottal release from high lung volumes that are close to total lung capacity (Cotes, 1993).

According to Bach (1993), normal pre-cough volumes are typically 85-90% of inspiratory capacity and the normal cough has a volume of 2.3 ± 0.5 L. Although cough volume was not measured in this study, the baseline mean FVC was 2.22 L or 58% average for predicted values and 23 out of the 29 participants in this study had FVC function within this therapeutic range for coughing. Therefore it is plausible that pre-cough inspiratory volumes also increased after the LVR treatment. In recent study on cough augmentation using a volume-controlled ventilators with 179 patients with respiratory insufficiency (including two patients with ALS) (Toussaint, et al. 2009) the criteria used to judge the effectiveness of breath-stacking was an immediate increase of 10% in the unassisted FVC. Toussaint et al. also examined the degree to

which baseline FVC values predicted effective outcomes with cough augmentation.

They found that with increasing FVC, the PCF benefit from breath stacking increases in general; however this relationship was not seen in a subgroup of patients with an

FVC <.340 L).

Based on the literature, relatively small short-term gains of .203 liters in FVC (or 9.1%) at time 2 in the current study may have been enough to facilitate improved coughing at time 3 especially when we consider that in this experiment the T2 FVC tasks measures were completed only a few minutes before the T3 PCF data. One of the procedural limitations of this study was that the SnP and FVC measures were the last tasks performed in each condition of the study and may also have been differentially affected by fatigue. The same factors that lead to improved compliance of the lung and chest wall may after LVR would likely enhance pre-cough inspiratory volumes and lead to less R_{aw} in the form of both volume-related and flow related airway collapse during coughing and forced expiration.

A variety of spirometry tests can be used measure R_{aw} and judge the extend and location of flow limitations. For example, the average forced expiratory flow rate at 200 and 1200 ml is used clinically to estimate the R_{aw} offered from larger airways during the effort-dependant portion of a maximal expiratory volume-flow loop. The average flow at 25% and 75% of the total volume is used to judge the integrity of the medium to small airways during forced expiration and coughing (Des Jardins, 2000).

Compliance of Small Conducting Airways. The third set of R_{aw} factors that may have contributed to the LVR treatment effect are changes in the compliance of small conducting airways that lead to improved airflow velocities. During the LVR

treatments, the distensible components of noncartilaginous airways (i.e., bronchioles and terminal bronchioles) may also be stretched and distorted by the high transmural pressures generated during LVR treatment session and especially during the compressive phase of augmented coughing trials. According to the wave mechanics theory, the maximal rate at which a pulse wave can be transmitted along the airway is determined by an interaction between the compliance of airway and the acceleration of the gas. Distensible airways stretch as the pulse wave passes through and this offsets the drop in pressure (due to the Bernoulli effect) thereby reducing the likelihood of flow limitations in the smaller airway (Cotes, 1993). When secretions are retained in the airway, the optimal locations for choke points are in the large bronchial airways. The downstream portion of the conducting airway may have to be cleared of endomural obstructions before sufficient flows can be generated to mobilize secretions in the smaller distal airways.

Improved compliance in the airways in conjunction with the previously discussed hysteresis properties of the lung and chest wall may offer a mechanical advantage during the compressive phase of coughing and airway clearance. As previously discussed, the initial portion expiratory limb of the pressure-volume curve remains elevated longer following treatments that improve compliance and elastance of the lung and chest wall. These short-term, time – dependent effects may offer patients who are slow or less coordinated with coughing and airway clearance more time and higher sustained lung volumes to perform sufficient compression to produce a strong cough. The hypothesis is that improved overall compliance of the respiratory system allows patients to better compensate for weak expiratory and laryngeal

muscles muscle while producing dynamic compression on the conducting airway and generating adequate intrathoracic pressure to clear the airway.

Expiratory Muscle Function. Expiratory muscle function plays a significant role in determining the effectiveness of coughing. Changes in the contractile forces generated during expiration may have contributed to the positive peak flow outcomes observed in this study. Research has shown that patients with ALS and expiratory muscle weakness have a preferential reduction in PCF rates and a slower rise time on the effort-dependant portion of a maximal expiratory volume-flow loop (Polkey, Lyall, Green, Leigh & Moxham, 1998). Expiratory muscles are not active during normal tidal breathing and are only recruited for periodic deep breaths and for forced expiration and coughing. Mild to moderate expiratory muscle weakness often goes undetected in patients with ALS as the sigmoid shape of the lung pressure-volume curve can be well preserved despite moderate respiratory muscles weakness (Fitting et al., 1999). Abdominal expiratory muscles (i.e., interior and exterior obliques and the transverse abdominis) provide the bulk of the expiratory muscles forces generated during coughing (DiMarco, Kowalski, Supinski, 1999). In patients with ALS, cough effectiveness may also be limited by paradoxical movement caused by abdominal muscle weakness during contraction of the chest wall via the internal inter-costals. (Boitano, 2006).

LVR has also been described as a passive range of motion exercise for the chest wall (Kang et al., 2005). The thorax may be realigned after the maximum insufflation and in a more normal position after having displaced abdominal contents downward, maximizing the stored tension-recoil forces of the ribs. Proponents of

LVR have claimed that the larger lung volumes and the accompanying chest wall expansion during and after LVR may also optimize the length, tension and contractile forces generated by the expiratory muscles in both the chest wall and the abdomen during coughing. Coughing involves a coordinated sequence of inspiratory muscle contractions, laryngeal valving, and expiratory muscle contraction. Without specific measures of expiratory muscle strength (e.g., maximal expiratory mouth pressures or surface EMG) in conjunction with standardized respiratory tests of pressure, volume and flow loop testing, it is difficult to determine the relative contribution of changes in expiratory muscle function to the outcomes of this study. The lack of any significant changes in inspiratory muscle strength after treatment, as measured by SnP, suggest that the underlying treatment mechanisms lie elsewhere, including expiratory muscles and/or lung and chest wall compliance, and R_{aw} during coughing.

LVR and Dysphagia Management

PCF as measured during the supraglottic swallow maneuver increased from baseline to time 2 and time 3. Increased PCF during the swallow maneuver translates into more effective airway clearance and safer swallowing. For many patients with neurological disorders such as ALS, dysphagia is high risk condition associated with adverse health outcomes such as malnutrition, dehydration and pneumonia. In patients with ALS, swallowing difficulty may also be associated with dyspnea, drooling and upper airway secretion encumbrance as well as an increased likelihood of laryngospasm.

Groher (1994) refers to a ‘vicious cycle’ of inter-related problems associated with dysphagia, protein-energy malnutrition and respiratory compromise that is

particularly relevant to ALS. Respiratory compromise exacerbates dysphagia, which in turn leads to poor nutrition and protein-energy malnutrition, which then causes increased respiratory compromise. Therefore, the clinician must deal with one, or all, of these factors to break the cycle (Groher, 1997) and improve health and well-being of the patient. The use of LVR to facilitate safe swallowing is a promising approach to breaking this cycle. By targeting respiration to improve airway clearance, patients may have improved swallowing ability and decreased risk of aspiration for up to 30 minutes following treatment. Although training in airway clearance is described in the literature, little evidence has been available to support their use with patients who have ALS.

Patient Perspectives on LVR

In the current study, participant perspectives on manual insufflation were solicited through a semi-structured interview and completion of a Likert-type rating scale. In the pilot study (Cleary et al., 2008), the perspectives of 11 patients with ALS were generally positive, with reports of less anxiety about breathing and better ability to clear secretions. Whereas some of those positive perceptions were replicated in the current study, the general findings related to patient perceptions are best described as mixed.

The majority of participants had positive perceptions of LVR's effect on cough strength and the ability to maintain a clear airway, perceptions that were consistent with the quantitative findings of increased PCF after LVR treatment. However, approximately 70% of the sample reported that they did not clear any mucous secretions from the lungs or throat during LVR therapy sessions. This result

seems to contradict the perception of the majority of participants (78%) who reported that LVR helps them to maintain a clear airway. These seemingly contradictory findings may be explained by the characteristics of the study participants.

As a group, the participants were characterized as having only minimal problems handling secretions, as measured by scores on the saliva severity scale of the ALSFRS-R and SWAL-QOL. Therefore, at this stage of the disease process, the participants are likely not dealing with secretion management issues on a regular basis. As such, they would not produce copious amount of mucous that would be obvious during LVR therapy.

In addition, the assumption that LVR would help alleviate fears related to choking was not substantiated, with only 21.4% of the sample indicating that LVR reduced their fear of choking. The participants in this study reported only mild to moderate psychological burden (i.e., anxiety) related to choking and thus would not be overly fearful at this stage of mild dysphagia and respiratory compromise. Later in the disease process, however, as patients with ALS begin to experience moderate to severe dysphagia and dyspnea, they often express fear of choking or suffocating and this anxiety can have a profound impact on quality of life (Mitchell & Borasio, 2007). Clinicians may help to relieve these fears and improve function through counseling and rehabilitation using LVR, airway clearance and safe swallowing maneuvers.

These qualitative findings highlight the importance of individualized care plans and appropriate timing of respiratory interventions. Because of the progressive nature of ALS and the associated short life expectancy of most patients, multidisciplinary palliative care must be initiated at the time of diagnosis. Although

palliative care is a term that is often considered synonymous with end-of-life care for patients in the terminal phase of their disease (Borasio, 2001), current conceptualizations of palliative care include other components. In addition to terminal care, Borasio describes palliative care as comprising communication, symptom control, and rehabilitation. The term rehabilitation “might be unexpected in this context, ...” (p.532) yet symptomatic treatment can involve active rehabilitation, as in the case of LVR. In the context of ALS, rehabilitation involves techniques to promote optimal functioning despite increasing impairments that accompany disease progression (DalBello-Haas, Florence, & Krivickas, 2008). These authors note that maximizing mobility, independence with activities of daily living, and speech are common goals for patients with ALS. Notably, the goals are not based on restoring function or curing patients. Thus, the rehabilitation focus on reducing symptoms without changing the underlying condition is consistent with contemporary definitions of palliative care.

The best time to initiate LVR will vary depending on the nature and severity of the respiratory impairment as well as the patient’s willingness to engage in the therapy. In clinics where LVR is used, it is recommended that the treatment be initiated early, when patients present with a PCF of <280 L/min, to capitalize on higher lung functions. Starting LVR earlier in the disease process may help stave off respiratory decline by maximizing the elastic properties and contractile forces of striated respiratory muscles. Given the limited life expectancy of individuals diagnosed with ALS and the high likelihood that patients will suffer from a compromised airway, promoting airway protection and clearance is a clinical priority.

Limitations of the Study

The use of a repeated measures cross over design was appropriate for the research questions of interest. The design has many benefits, including the ability control for inter-subject variability by having participants serve as their own controls. However, the primary weakness associated with such a design is the risk of carryover effects. The likelihood of carryover effects of the LVR treatment was minimized by counterbalancing treatments and by ensuring a washout period of at least 24 hours between conditions. However, practice effects gained during trials with the airway clearance and swallowing maneuvers may have moderated the treatment effects between conditions.

Variability in the duration and performance of LVR may also have affected study results. In the current study 13 participants had been performing LVR for six weeks or less and had received limited follow-up training prior to the start of the study. Seven requested assistance with LVR after completion of the study: two requested face masks, three wanted help to decrease the amount of air swallowed during LVR, one wanted strategies to cope with thin secretions that caused coughing during LVR and one participant reported that his reflexive laugh interfered with his treatment (pseudobulbar affect). These reports not only have the potential to impact responsiveness to LVR therapy, but they highlight the need for ongoing monitoring, follow-up training and adaptations as patient needs and abilities change over time.

The interviews and rating scales used to solicit participants' perspectives about LVR were designed for the purposes of the study and would benefit from modifications. In an effort to reduce the response burden placed on participants, some

items that were included to help with internal consistency were deleted from the rating scale. The final version of the rating scale did not allow full examination of patient perceptions, with some items being poorly worded and difficult to understand. A qualitative research design, method and analysis would have allowed in-depth examination of patient perceptions, which was not possible in the current study.

Generalizability of the findings is also an issue. In the case of this thesis research, the goal was to determine the presence of treatment effects that could then be reasonably expected for the larger population of individuals with ALS. Strict inclusion criteria and the relatively mild respiratory symptoms of the study participants may limit the external validity of the study's results. That is, the results may be particularly applicable only to those individuals with ALS who have similar characteristics as participants in the study sample. Of significant importance is the issue of cognitive impairment among individuals with ALS and the effect of this impairment on the ability to perform LVR as well as volitional airway clearance strategies and safe swallow maneuvers. Although prevalence estimates vary greatly, Ringholz et al. (2005) report that, after reviewing records from more than 250 patients with probable or definitive ALS, 40-50% had some degree of cognitive impairment. Cognitive deficits among patients with ALS are associated with poor adherence to treatment recommendations (Neary et al., 1993) and therefore, might affect outcomes of LVR. Even with some degree of cognitive impairment, many people with ALS will likely exhibit the ability to learn; however, cognitive impairment and its correlation with outcomes of LVR is a topic for future investigation.

Future Research

To date, no formal efficacy study using a randomized controlled trial (RCT) has been conducted on LVR. However, an RCT may not be the most appropriate next step in this line of research. The preponderance of research evidence on LVR, including the results from the current study, point to positive outcomes on airway clearance. Therefore, withholding LVR in a standard RCT design may be present ethical issues, particularly in consideration of the short life-expectancy of individuals with ALS.

An alternative to a RCT would be to compare the effects of LVR to a placebo treatment in a 2 x 2 crossover design incorporating short wash-out periods between treatment and comparison conditions. The use of a placebo treatment would improve internal validity of the study by minimizing the threat of selection bias or the effect of differential effort on behalf of the participants. A placebo treatment condition consisting of intensive speech and voice exercises was used by Cleary and colleagues (2007) to judge the effectiveness of volitional breath-holding technique while swallowing and could be adapted for use in future studies. Comparison of LVR and other manual cough augmentation treatments to mechanically-assisted insufflation techniques is also a plausible next step in a program of research in this area.

Outcomes of LVR treatment should also be investigated. Factors that influence response to treatment (e.g., cognitive impairment, disease severity), the relationship between intensity and outcomes (dose-response), the duration of the treatment effect, and treatment effects on markers of respiratory health (e.g.,

atelectasis, pneumonia, CO₂ retention) and quality of life are important targets for further research.

In terms of dysphagia management, more research is needed to support the use of peak cough device as a clinically relevant approach for measuring risk of airway compromise while swallowing. Future research on LVR should compare PCF data with data gleaned from more traditional methods to assess swallowing biomechanics such as videoflourscopy and nasoendoscopy. For example, videofluoroscopy could be used to quantify changes in swallowing physiology and bolus flow as the result of treatment. Nasoendoscopy could be used during the swallow to visualize laryngeal closure and pharyngeal constriction, as well as to measure changes in secretion clearance from the throat. Changes in pulmonary clearance could be assessed simultaneously with chest x-rays, chest auscultation, sputum counts, pulse oximetry/oxygen saturation.

Another clinically relevant future research question relates to the potential influence of LVR on breathing mechanics while swallowing (i.e., respiratory phase, rate, depth of tidal breathing while eating). Specifically, the question remains: Does LVR promotes a more typical pattern of breathing while swallowing? In the pilot study (Cleary et al., 2007) we used a chest strap as a measure of chest wall movement and accelerometry to detect pharyngeal swallowing. The results with three participants were positive: there appeared to be a more typical pattern of breathing more frequently during expiration as a result of treatment. However, these tasks were cumbersome and too time consuming to include in the current study and thus should be examined in the future.

Conclusions

The findings of this study supplement the growing literature on outcomes of manual insufflation techniques for promoting improvements in pulmonary and respiratory function of individuals with ALS. The positive effects of LVR on coughing and other airway clearance behaviours, as well as the supraglottic swallow, are important outcomes for patients with ALS and respiratory compromise. Evidence-based practice requires consideration of best research evidence, in conjunction with clinical expertise and patient and family desires, when providing care. A continued focus on research related to respiratory and swallowing symptom management is necessary to ensure quality of life and care of individuals with ALS and their families.

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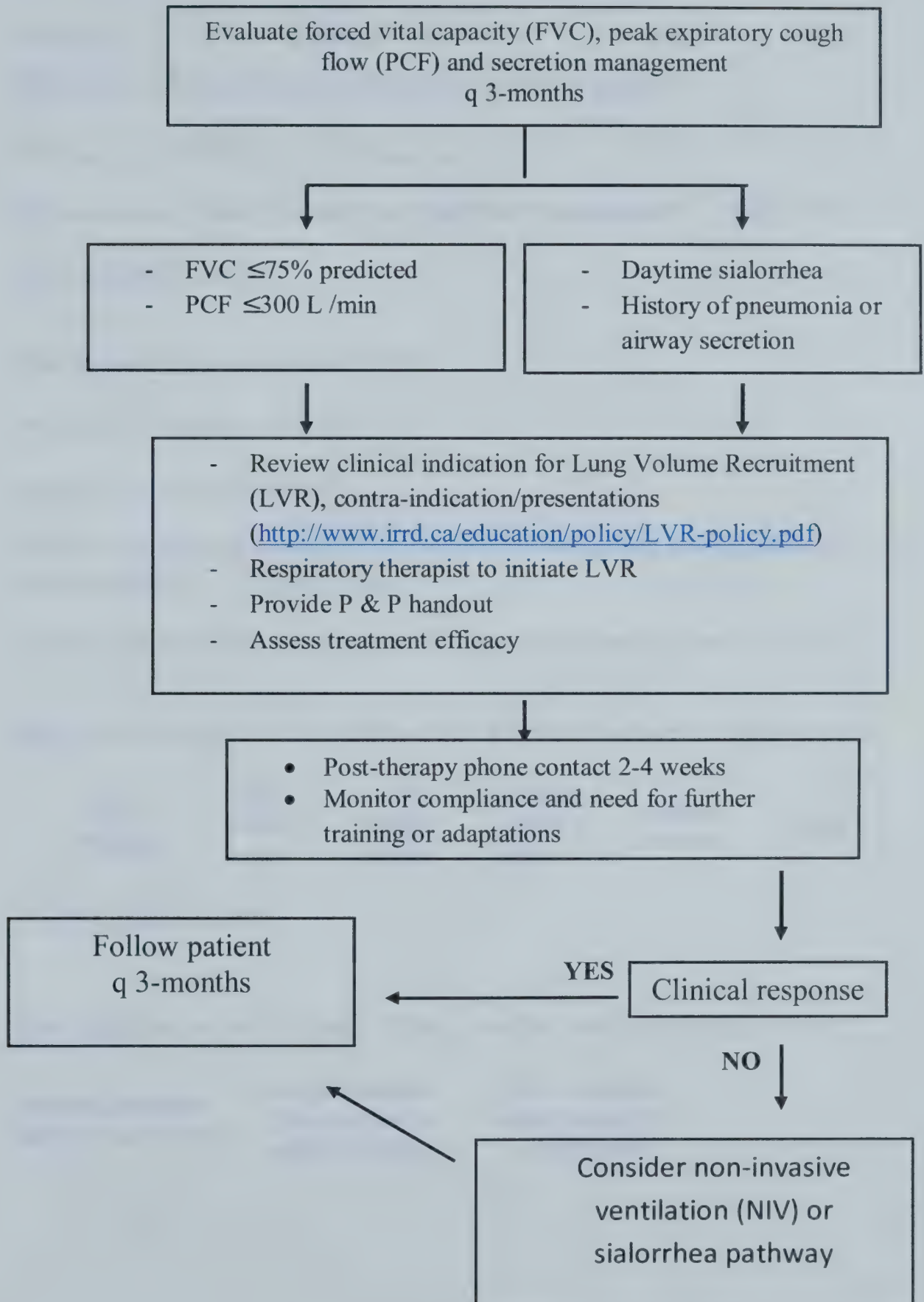
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Appendix A. LVR Initiation Algorithm



Appendix B. LVR History and Use of LVR Questionnaire

Start Time:

Participant:

Location:

Date:

When did you first start doing LVR? (When were you trained?)

Day _____ Month _____ Year _____

Do you have any tricks that help you to perform this technique? YES / NO

If YES, please describe:

How frequently do you perform LVR?

Average # of sessions per day: _____

Average # of trials per session: _____

Are there any triggers, or changes in how you are feeling that prompt you to do LVR more frequently? YES / NO

If YES, please describe (i.e. congestion, shortness of breath, secretions, etc.):

What time of the day do you typically do LVR? (Circle as many as apply to you)

Upon awaking	AM before lunch	PM before dinner	Evening after dinner	Before bedtime	Other
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If Other, please describe:

How consistent are you in doing LVR on a week to week basis? (Circle one)

Very Consistent (same # each week)	Some Variability (miss a session once in a while)	Not Consistent (some weeks lots, others none)
1. How often do you practice? 2. How often do you practice? 3. How often do you practice? 4. How often do you practice? 5. How often do you practice? 6. How often do you practice? 7. How often do you practice? 8. How often do you practice? 9. How often do you practice? 10. How often do you practice?	1. How often do you practice? 2. How often do you practice? 3. How often do you practice? 4. How often do you practice? 5. How often do you practice? 6. How often do you practice? 7. How often do you practice? 8. How often do you practice? 9. How often do you practice? 10. How often do you practice?	1. How often do you practice? 2. How often do you practice? 3. How often do you practice? 4. How often do you practice? 5. How often do you practice? 6. How often do you practice? 7. How often do you practice? 8. How often do you practice? 9. How often do you practice? 10. How often do you practice?

How much mucous do you currently clear from your lungs during a typical LVR session? (Circle one)

A little	A lot	It varies	None
(1 teaspoon or less)	(2 or more teaspoons)	(sometimes lots, others a little)	(nothing comes out)

How would you describe these lung secretions? (Circle one)

Thin	Thick	A combination
(clear, wet)	(not clear, glob-like)	(some gross mixture of the two)

How much mucous do you currently clear from your throat during a typical LVR session? (Circle one)

A little	A lot	It varies	None
(1 teaspoon or less)	(2 or more teaspoons)	(sometimes lots, others a little)	(nothing comes out)

How would you describe these throat secretions? (Circle one)

Thin	Thick	A combination
(clear, wet)	(not clear, glob-like)	(mixture of the two)

Typically how do you feel after doing a LVR session? (Circle as many as apply to you)

Tired	Short of Breath	Cleared Airway	Refreshed	Other
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If other, please describe:

The next few questions are designed to find out how lung volume recruitment (LVR) therapy affects your ability to breath, cough, swallow, speak and manage your secretions.

Please read the statements below about LVR therapy and indicate whether you agree or disagree by circling a corresponding number.

	Strongly Disagree	Disagree	Uncertain/ Neutral	Agree	Strongly Agree
LVR therapy helps me to keep my airway clear	1	2	3	4	5
LVR helps me to clear thin secretions from my throat	1	2	3	4	5
LVR helps me to clear thick mucous from my throat	1	2	3	4	5
LVR helps me to clear thick mucous from my lungs	1	2	3	4	5
LVR does not improve the strength of my cough	1	2	3	4	5
LVR improves the loudness of my voice	1	2	3	4	5
LVR improves the quality of my voice	1	2	3	4	5
LVR therapy makes me more anxious about my breathing	1	2	3	4	5
LVR therapy makes me less anxious about managing excess secretions	1	2	3	4	5
I have less fear of choking because of LVR therapy	1	2	3	4	5
I have less fear of being very short of breath because of LVR therapy	1	2	3	4	5

	Excellent	Very Good	Good	Fair	Poor
Please estimate the average strength of your cough before you do LVR	1	2	3	4	5
Please estimate the average strength of your cough immediately after you do LVR	1	2	3	4	5
Please estimate the quality of your voice before you do LVR	1	2	3	4	5
Please estimate the quality of your voice immediately after you do LVR	1	2	3	4	5

Are you currently doing Bi-Pap breathing treatments? YES / NO

If NO, please return the questionnaire to the researcher. Thank you.

When did you first start doing Bi-Pap? Day _____ Month _____
Year _____

How many hours a day do you wear your Bi-pap mask? _____ hours

What time of the day do you typically do Bi-Pap? (Circle as many as apply to you)

Upon awaking AM before lunch PM before dinner Evening after dinner Before bedtime While Sleeping Other

If Other, please describe:

Has LVR therapy improved your tolerance of the Bi-Pap treatments? YES / NO

Do you sleep any better with the Bi-Pap mask since receiving LVR therapy?
YES/NO

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